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Selected Abstracts
on

POTENTIAL OCCUPATIONAL CAUSES OF CANCER

II. THE URINARY TRACT

Richard R. Monson, M.D., Sc.D.
Consulting Reviewer

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of the National Cancer Institute

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INTRODUCTION

This ONCOLOGY OVERVIEW on occupational causes of urinary tract cancer includes abstracts selected from the CANCERLIT database referencing articles published mainly from 1982 to mid-1986. The last CANCERLIT update searched for this ONCOLOGY OVERVIEW was June, 1986.

THE STRATEGY USED TO RETRIEVE THESE ABSTRACTS CAN BE REQUESTED FROM THE CIDAC-CCB AND ENTERED ON ANY MEDLARS/MEDLINE TERMINAL SYSTEM TO UPDATE REFERENCES IN THIS AREA.

The scope of this OVERVIEW covers the epidemiological/etiological studies of occupation-associated cancer of the urinary tract and the prostate, carcinogenicity studies of occupation-related chemicals on animal urinary tract and prostate, as well as the genetic/biochemical/metabolic aspects of urinary tract carcinogenesis induced by occupation-related chemicals. A small section deals with the interrelationship of smoking with occupational exposure in causing urinary tract cancer. Urinary tract, as used here, includes bladder, kidney, ureter and urethra.

Studies on the occupational causes of respiratory tract cancer published between 1982 and 1985 can be found in a previous ONCOLOGY OVERVIEW, Selected Abstracts on "Potential Occupational Causes of Cancer. I. The Respiratory Tract Cancer", April 1986, PB 86-922902.

This present OVERVIEW was prepared by Esther I-hsin Chow, Ph.D., Subject Specialist of the CIDAC for Carcinogenesis and Cancer Biology, Information Ventures, Inc., Philadelphia, PA. Richard R. Monson, M.D., Sc.D., Department of Epidemiology, Harvard School of Public Health, Boston, MA was the Consulting Reviewer and wrote the Editorial Commentary.

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EDITORIAL COMMENTARY

BLADDER CANCER

RUBBER INDUSTRY

The role of occupation in the etiology of bladder cancer was first suggested in 1895 by Rehn (1,2). He reported several cases of bladder cancer among workers in the dyestuffs industry and suggested that aniline dyes were responsible. Later work by Case et al. in the British dye industry demonstrated that two aromatic amines, benzidine and 2-naphthylamine, were the etiologic agents (3). At the same time, Case and co-workers evaluated the excess occurrence of bladder cancer among workers in the British rubber industry (4,5). This work established beyond reasonable doubt that the 2-naphthylamine used as an anti-oxidant in making rubber caused the excess cases of bladder cancer among British rubber workers.

In contrast, studies of American rubber workers have shown little or no excess bladder cancer (6-9). Since the beginning of the rubber industry in America, chemicals other than 2-naphthylamine have been used as anti-oxidants. Thus, the difference in occurrence of bladder cancer between the British and the American rubber industries apparently relates to the difference in the type of anti-oxidant used.

In 1949 2-naphtylamine was removed from use in the British rubber industry (10) and subsequent studies of British rubber workers have not shown any excess occurrence of bladder cancer (11,12). Data from rubber industries in other countries are sparse (10), but in general, there is no indication that the degree of excess bladder cancer that occurred in the British rubber industry was seen elsewhere.

The papers cited in this Overview (Sections I.B.1 and I.C.1) are in general accord with the hist orical perspective. Of particular note are the studies of Schulte et al. (13) and Rubino (14) in the United States and in Italy. Each author reports an excess occurrence of bladder cancer among persons who worked with 2-naphtylamine or with benzidine. Thus, even though almost 40 years have passed since the hazard of these chemicals was definitively recognized, excess cases of bladder cancer continue to occur.

OTHER CHEMICALS IN INDUSTRY

While benzidine and 2-naphthylamine have clearly been shown to cause bladder cancer, there is less evidence concerning other industrial exposures. In 1971 Cole et al. performed a population-based case-control study of workers in the leather industry in eastern Massachusetts and reported an increase in cases of bladder cancer (15). While this association was in accord with previous studies, no specific chemicals have been identified.

A number of recent case-control studies are reviewed in this Oncology Overview. Of particular note is the National Bladder Cancer Study that was conducted in the United States during the late 1970's (16,17). This was a population-based case-control study of almost 3000 persons with bladder cancer that was initiated in response to the concern about the association between artificial sweetners and bladder cancer. No general chemical exposure or specific industry was found to be clearly associated with an excess occurrence of bladder cancer. However, an overall odds ratio of 1.6 was found for men employed for at least 10 years as truck drivers (18). A similar odds ratio was found in an independent case-control study of truck drivers in rural New England (19). The culprit in these cases may be motor exhaust compounds.

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Other major sources of data on the relation between occupation and bladder cancer derive from case-control studies conducted in New Jersey (20), Montreal (21), and Great Britain (22). While in each study associations with specific occupations were reported, there was little consistency across the studies. Also, no specific suspect chemical was identified. Follow-up studies among workers in the aluminum industry have shown an excess occurrence of bladder cancer (23,24). Exposure to polycyclic aromatic hydrocarbons has been suggested to be responsible.

PROSTATE CANCER

CADMIUM

An association between occupational exposure to cadmium and prostate cancer was reported in two early studies (25,26). In each of these studies four cases of prostate cancer were observed where only 1.7 cases were expected. Based on this work it was postulated that cadmium may influence the risk of developing prostate cancer (27). However, additional follow-up of these cohorts, as well as studies on other groups of men exposed to cadmium has yielded mixed results (28-30). While on balance excess prostate cancer appears to have occurred among men exposed to cadmium, the relative risk is per haps 2-3 rather than greater than 4.

Some non-epidemiologic studies strengthen the argument that the association between cadmium and prostate cancer is causal. The amount of cadmium in prostate tissue was measured and found to be lowest in normal prostate tissue, intermediate in adenoma, and highest in carcinoma (31). In a study in which cadmium was injected into the prostate of rats, hyperplasia or carcinoma was observed after 270 days (32).

OTHER CHEMICALS

Based on rather sparse data, a number of other occupational exposures have been reported to be associated with prostate cancer (27,33). No correlation is sufficiently compelling, however, to compare with that of cadmium and prostate cancer.

KIDNEY CANCER

In one case-control study an association between cadmium and kidney cancer was reported (34), however, in follow-up studies of cadmium workers, evidence was insufficient to suggest any correlation (29,30). An association between exposure to gasoline and kidney cancer was suggested (35), but the authors emphasize that additional data are needed. Excess cases of kidney cancer were reported in persons working around coke ovens or exposed to asbestos (2), but the specifics of these relationships is unclear.

FUTURE DIRECTIONS

While case-control studies in human populations will continue to be of value to suggest associations between occupational exposure and cancers of the urinary tract and prostate, it seems likely that the most useful information on occupational causes of these cancers will come from follow-up studies of cohorts of persons who work with specific chemicals. Carcinogens with the strength of 2-naphthylamine are unlikely to be present in the environment of present-day workers. It is expected that they will be better controlled than in the past. A very accurate measure of exposure levels of hazardous chemicals is needed to relate them to the occurrence of cancer and other diseases. Prospective monitoring of workers exposed to potentially hazardous chemicals is needed to determine the relatively weak correlation with disease that may be expected from the compounds.

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ABSTRACTS

I.

EPIDEMIOLOGY AND ETIOLOGY OF POTENTIAL OCCUPATIONAL CANCER OF THE URINARY TRACT AND THE PROSTATE

A.

General Occupational Studies

1.

Studies in the United States and Canada

1. OCCUPATION AND BLADDER CANCER IN BOSTON, USA, MANCHESTER, UK, AND NAGOYA, JAPAN

Morrison AS. Ahlbom A. Verbeek WG. Aoki K. Lack I. Ohno Y. Obata K

Department of Epidemiology, Harvard University, School of Public Health, Boston, MA 02115.

J Epidemiol Community Health; 39(4):294-300 1985

Relations between occupational history and the development of cancer of the lower urinary tract ('bladder cancer') were evaluated in Boston, Massachusetts, USA, Manchester, UK, and Nagoya, Japan. Population-based series of incident cases and controls were identified and interviewed in each area. The present analysis was limited to men and was based on 430 cases and 397 controls in Boston, 399 cases and 493 controls in Manchester, and 226 cases and 443 controls in Nagoya. In Boston, elevated risk of bladder cancer was associated with employment related to dyes (relative risk = 2.1; 90% confidence interval, 0.9-5.1), leather (1.7; 1.1-2.6), paint (1.5; 0.9-2.4), or organic chemicals (1.6; 1.1- 2.5). In Manchester, elevated risk was associated with work related to leather (3.2; 1.3-8.0) 1.8; 9-3.6). No clear association was observed between occupation and risk in Nagoya. Elevations in risk related to occupation generally were stronger in men under 65 years of age compared to older men. Differences from place to place in associations between occupation and risk may be the result of differences in the exposures to hazardous agents that jobs with the same title involve.

2. CASE-CONTROL STUDY OF BLADDER CANCER IN NEW JERSEY. I. OCCUPATIONAL EXPOSURES IN WHITE MALES

Schoenberg JB. Stemhagen A. Mogielnicki AP. Altman R. Abe T. Mason TJ

Division of Epidemiology and Disease Control, New Jersey State Department of Health, Trenton.

JNCI; 72(5):973-81 1984

The occupational bladder cancer risk for New Jersey white males was estimated with the use of both industry-job title-based and exposure-based analyses of data from 658 incident cases and 1,258 general population controls. The overall bladder cancer risk attributable to occupational exposures was estimated as 20-22%. A wide variety of employment categories and exposures contributed to this risk. Odds ratios were significantly high for employment as garage and gas station workers and food counter workers and/or cooks and for exposure to leather, rubber, paint, printing ink, and other organic compounds. Odds ratios for textile mill workers, chemical workers, and metal workers for the a priori high-risk employment category and odds ratios for those exposed to dyes, chlorinated compounds, and rubber showed significant differences between younger and older subjects. Bladder cancer risk associated with occupational exposures was not limited to persons with initial exposures before 25 years of age. However, there was significantly decreasing risk for bladder cancer with increasing age at first exposure for chemical workers and metal workers and for the a priori high-risk materials and metals. Drivers and/or deliverymen and miscellaneous laborers had significantly increasing bladder cancer risk with increasing duration of employment.

3. BLADDER CANCER MORTALITY IN NEW JERSEY COUNTIES, AND RELATIONSHIP WITH SELECTED ENVIRONMENTAL VARIABLES

Najem GR. Louria DB. Najem AZ

Department of Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School, Newark.

Int J Epidemiol; 13(3):273-82 1984

Age-adjusted mortality rates for bladder cancer were calculated for the 21 New Jersey (NJ) counties (USA) during the period 1968-1977, and compared with the period 1950-1969, with the Surveillance, Epidemiology and End Results (SEER) survey and with cancer mortality in the US 1973-1977. The county rates were also correlated with: the rates of low birth weight, birth defects, infant mortality; chemical waste disposal sites; annual per capital income; per cent of the population working in the chemical industries; density of population and urbanization indices of 21 NJ counties. Age-adjusted bladder cancer mortality rates in 95% of NJ counties were higher than national and SEER area rates. The overall NJ State rates for four subgroup populations were highly significantly (p less than 0.001) greater than the national rates. There was a statistically significant correlation between bladder and lung cancer mortality among females in 21 NJ counties which may suggest a common risk factor - namely cigarette smoking. There was no such correlation between bladder and lung cancer mortality among males. There was a statistically significant association between bladder cancer mortality in individual counties and the percentage of the adult population working in the chemical industries.

4. RISK FACTORS FROM A POPULATION-BASED CASE-CONTROL STUDY OF RENAL CANCER

McLaughlin JK

Dept. of Epidemiology, Johns Hopkins Sch. of Hygiene and Public Health, Baltimore, MD 21205

Adv Med Environ Toxicol; 7:227-44 1984

Results are presented of a population-based case-control study of renal cancer (495 cases of renal cell carcinoma, 74 cases of cancer of the renal pelvis, and 697 controls). Cases were restricted to residents of the Minneapolis-St. Paul standard metropolitan statistical area who were white and who were initially diagnosed during the period 1 January 1974 to 30 June 1979. Controls 30-64 yr of age were obtained from telephone listings, and those 65-85 yr of age were obtained using an age- and sex-stratified systematic sample pro-

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vided by the Health Care Financing Administration. For both types of renal cancer and in both sexes, cigarette smoking was found to be a statistically significant risk, which increased with consumption as measured by pack-years. An estimated 30% of the renal cell carcinomas in males and 24% in females were attributable to the cigarette smoking. For cancer of the renal pelvis, 82% of the cases among males and 61% of those among females were related to cigarette use. High relative adult wt was a major risk factor (odds ratio, 2.31) for renal cell carcinoma among women; other risk factors for the renal cell carcinoma included long-term use of phenacetin-containing analgesics (odds ratio 3.9 for men, 3.7 for women), ethnic background (especially German; odds ratio 1.5 for men, 2.2 for women), heavy meat consumption, and exposure to petroleum, tar, and pitch products. Other risk factors for cancer of the renal pelvis included long-term use of analgesics and a number of occupational exposures; the use of estrogen products and heavy tea consumption among women also was associated with renal pelvis cancer, although the significance of these findings remains to be clarified. (31 Refs)

5. OCCUPATION AND CANCER OF THE LOWER URINARY TRACT IN DETROIT

Silverman DT. Hoover RN. Albert S. Graff KM
Biometry Branch, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Md.
JNCI. 70(2):237-45 1983

The relationship between occupation and cancer of the lower urinary tract in Detroit was examined by means of a population-based case-control study conducted as part of the National Bladder Cancer Study. Three hundred three white male patients with transitional or squamous cell carcinoma of the lower urinary tract and 296 white male controls selected from the general population of the study area were interviewed to obtain lifetime occupational histories. Our findings suggested that truck drivers have a significant increased risk of lower urinary tract cancer [relative risk = 2.1; 95% confidence interval (CI) = 1.4-4.4]. A significant trend in risk was apparent with increasing duration of employment as a truck driver (P = 0.004); the relative risk estimated for truck drivers employed at least 10 years was 5.5 (CI = 1.8-17.3). Truck drivers with a history of operating vehicles with diesel engines experienced a significant elevated risk compared to non-truck drivers (relative risk = 11.9; CI = 2.3-61.1), but whether the increased risk observed among truck drivers was attributable to diesel exposure could not be evaluated. Nonsignificant excess risks were also seen for tool and die makers as well as for workers in several other industries and occupations. Employment in the motor vehicle manufacturing industry was associated with no significant excess risk of lower urinary tract cancer (relative risk = 1.1, CI = 0.8-1.5).

6. ETIOLOGY OF CANCER OF THE RENAL PELVIS

McLaughlin JK. Blot WJ. Mandel JS. Schuman LM. Mehl ES. Fraumeni JF Jr
Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Md.
JNCI. 71(2):287-91 1983

A population-based case - control interview study of cancer of the renal pelvis (74 cases and 697 controls) conducted in the Minneapolis - St. Paul metropolitan area showed cigarette smoking to be the major cause of this cancer. The odds ratio (OR) for cigarette smoking was 7.6 among males [95% confidence interval (CI): 2.2-31.5] and 5.8 among females (95% CI: 2.0-17.3), with the OR exceeding 10 for heavy smokers of both sexes. Long-term use of analgesics and several occupational exposures were also found to be risk factors. In addition, there were unexpected positive associations among females for heavy tea consumption and for use of estrogen medications, although the significance of these relationships remains to be clarified.

7. BLADDER CANCER ETIOLOGY: A DIFFERENT PERSPECTIVE

Weinberg DM. Ross RK. Mack TM. Paganini-Hill A. Henderson BE
(c/o Ross), Unit, Southern California Sch. Medicine, Parkview Medical Building B-202, Los Angeles, CA. 90033
Cancer: 52(4):675-680 1983

The descriptive epidemiologic features of bladder cancer and lung cancer in Los Angeles County were studied for the period 1972-1976, using data from the Los Angeles County/ University of Southern California Cancer Surveillance Program. The incidence pattern for bladder cancer was found to differ markedly from the pattern observed for lung cancer. As expected, the descriptive pattern for lung cancer closely paralleled the known epidemiology of cigarette smoking, in addition, it was consistent with the expected pattern of an occupationally linked disease. In contrast, the pattern observed for bladder cancer indicated that factors other than cigarette smoking and occupational exposures may be etiologically important. The available descriptive epidemiology of coffee consumption, unlike that of cigarette smoking, is consistent with the pattern of bladder cancer occurrence in Los Angeles. Available analytic studies on the association of bladder cancer and coffee consumption are consistent with a causal relationship. (Author abstract) (35 Refs)

8. THE ETIOLOGY OF PROSTATE CANCER: WHAT DOES THE EPIDEMIOLOGY SUGGEST?

Ross RK. Paganini-Hill A. Henderson BE
Department of Family and Preventive Medicine, University of Southern California, Los Angeles.
Prostate: 4(4):333-44 1983

The two most important demographic characteristics of prostate cancer in Los Angeles are the high rates among blacks, which are two times those among whites and four times those among Asians, and the rapid increase in rates with age after age 40. Despite the high rates among blacks, a birth cohort analysis indicates that mortality rates among black men born after 1900 have decreased. In this report, epidemiologic and experimental evidence supporting each of three etiologic hypotheses - industrial exposure to cadmium, sexual transmission by an infectious agent, and endocrine factors - are reviewed. Evidence from descriptive data in Los Angeles suggests that only a small portion of cases might be attributable to industrial exposures. In a cohort study of Catholic priests, we found no deficit of prostate cancer mortality, strong evidence against sexual transmission of the disease. Experimental evidence and a limited amount of human data support an endocrine hypothesis. Preliminary results of a case-control study of prostate cancer are presented, but these results are unable to distinguish among these hypotheses further. This study finds a substantial protective effect of vasectomy, an event that is accompanied by reduced prostatic function and size, but this result is thus far statistically insignificant.

9. TRENDS IN CANCER MORTALITY AND EPIDEMIOLOGY

Miller AB
NCIC Epidemiology Unit, University of Toronto, Ontario, Canada.
Cancer: 51(12 Suppl):2413-8 1983

The increase in lung cancer in men has ceased at younger ages and is slowing at older ages. However, in women the

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increase continues and, by the end of this decade, lung cancer may be the most importa nt cause of cancer deaths in women. The incidence of prostate and breast cancer continues to increase, but mortality is stable, suggesting changes in diagnostic practices. Mortality from stomach cancer and from cancer of the cervix in women continues to fall. Increasingly, it is necessary to recognize the multifactorial causes of cancer, requiring detailed information on lifestyle, occupational, and sometimes residential histories to unravel etiology. Physicians need to understand the requirement for access to patients in order to obtain data for studies. Monitoring unexpected hazards will require linkage, particularly using the National Death Index. Such sources can be used with preservation of confidentiality while increasing knowledge for primary prevention.

10. BLADDER CANCER RISK FACTORS IN UTAH (MEETING ABSTRACT)

West DW
University of Utah Medical Center, Salt Lake City, UT
Advances in Bladder Cancer Research, January 5-8, 1983, Sarasota, Florida. National Bladder Cancer Project 112 pp., 1983.

The primary objectives of this case-control study are to: 1) examine the relationship between coffee consumption and bladder cancer; 2) examine the relationship between caffeine use and bladder cancer; 3) look for synergistic effects of coffee and caffeine with tobacco in relationship to bladder cancer risk; 4) identify reasons why the incidence of bladder cancer is higher in the urban areas of Utah than the rural areas; 5) determine why the incidence of bladder cancer has been increasing among older males in Utah, and 6) look for other variables that may be involved in the etiology of the disease, ie, saccharin, occupation, hair dyes, previous illnesses, etc. The coffee and caffeine variables are of special interest to this study since previous studies show inconsistent findings in terms of the association between these variables and bladder cancer. The population of Utah is ideal for the study of caffeine use and its relationship to disease since only about 50% of the residents of the state use coffee, and there is a large group of people who use decaffeinated coffee and/or caffeinated soft drinks while abstaining from cigarette smoking, alcohol, and regular coffee use. Cases were identified through the Utah Cancer Registry (1978-1982) which registers all cases of bladder cancer diagnosed in Utah. Controls aged 21-64 were selected by random-digit-dialing and those aged 65-84 were selected from the files of the Health Care Financing Administration. Twice as many controls as cases are selected, with controls having the same age and sex distribution as cases. Data has been cleared and analysis is now underway. Preliminary results will be available by early 1983. (no Refs)

11. BLADDER CANCER: SMOKING, BEVERAGES, OCCUPATION AND OTHER FACTORS (MEETING ABSTRACT)

Connolly JG, Chapman JA, Rosenbaum L, Rider WD
No affiliation given
Seventy-eighth Annual Meeting of the American Urological Association, Inc., April 17-21, 1983, Las Vegas, Nevada. American Urological Association, Inc. 330 pp., 1983.

In the early studies on the etiology of bladder cancer, there were potent carcinogens in the work place. This resulted in a large number of bladder cancers in certain high profile industries. The association between exposure to a compound and the development of bladder cancer was easily recognized. However, such carcinogens as Beta Naphthylamine, Benzidine, 4 Amino Biphenyl have mostly been removed or are on a restricted use. Recently there has been a proliferation of other industrial chemicals in use. A much larger proportion of the population is now being exposed to weaker carcinogens. These newer risks may be much lower for an individual and require longer latent periods, but given their more widespread use pose a greater overall carcinogenic threat. Generally, then, we are looking for much smaller effects than have been seen in the past, and the situation for epidemiological studies is more complex. Many case-control studies considering a wide variety of exposures have been reported recently. In these, only cigarette smoking has been associated with bladder cancer fairly consistently. Inconsistent associations have been found for coffee drinking, occupation, industrial chemicals artificial sweeteners, medical history, pipe smoking, education, water supply, consumption of cola, alcohol consumption and country of residence. Inconsistencies may result from the high correlations often reported for some variables. In a recent study completed by us, some 350 patients with bladder cancer were interviewed. We analyzed a great assortment of factors that could be etiologically important. Using multivariate analyses we have examined interactions between factors and their effects of the disease. (no Refs)

12. LIFE TIME OCCUPATION, SMOKING, CAFFEINE, SACCHARINE, HAIR DYES AND BLADDER CARCINOGENESIS

Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, Fernicola AP
Dept. Preventive Medicine and Community Health, Univ. Medicine and Dentistry New Jersey, New Jersey Medical Sch., 100 Bergen St., MSB-F516, Newark, NJ, 07103
Int J Epidemiol; 11(3):212-217 1982

A case-control study of bladder cancer in two northern counties of New Jersey was conducted to investigate a tumor that has been considered to be strongly associated with industrial and environmental exposures. The study population included 75 bladder cancer cases and 142 controls. Cases and control were matched for race, sex, age, place of birth and place of residence. Statistically significant associations with bladder cancer and risk ratios of greater than 2.0 were found for cigarette smoking and for working in dye, petroleum (fuel) or plastics industries. No statistically significant association was found for: cigar and pipe smoking; caffeine, saccharine and alcohol consumption; and life time occupational history of working in other than dye, petroleum and plastics industries. No statistically significant differences between cases and controls were found in family history of cancer. Risk ratios of at least 2.5 (but without statistical significance possibly because of sample size) were found for workers in rodenticide and printing industries, for cable workers and for cancer in the spouses of bladder cancer cases. Simultaneous multiple primary cancer sites were found in 9.3% of the bladder cancer patients; this is higher than the 0.2-8% reported in the medical literature. The life time occupational history of the bladder cancer cases points to industrial determinants: some are known (petroleum and dye industries) but the association with the plastics industry is new. If our findings are confirmed, investigations will be needed to determine whether any specific chemical or combination of chemicals used in the plastics industry is responsible for bladder cancer induction. (Author abstract) (26 Refs)

13. EPIDEMIOLOGIC SURVEY OF BLADDER CANCER IN GREATER NEW ORLEANS

Sullivan JW
1542 Tulane Ave., New Orleans, LA, 70112
J Urol; 128(2):281-283 1982

Primary ancestry of the patients and controls in this study was not statistically different but the Jewish population had a

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significantly increased incidence of bladder cancer. Over-all, a significantly greater number of patients smoked filtered cigarettes, began drinking artificially sweetened beverages at an earlier age, drank artificially sweetened beverages for a greater number of yr, consumed a greater number of glasses of artificially sweetened beverages weekly and related a history of urinary tract infections. A significantly increased incidence of bladder cancer was noted in individuals employed by certain types of companies, by certain job titles and by certain job material handled. Analysis of the data failed to show any significant difference in yr of consumption of coffee, amount of various types of coffee or tea consumed, consumption of various nonalcoholic and alcoholic beverages, including source of drinking water, use of hair dye, incidence of diabetes mellitus, family history of urinary cancer and a history of pelvic irradiation or bladder stones. (Author abstract) (4 Refs)

14. OCCUPATION AS AN ETIOLOGIC FACTOR IN RENAL CELL CARCINOMA (MEETING ABSTRACT)

Asal NR. Bryan JS. Geyer JR

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

This study was designed to investigate the significance of occupation as an etiologic factor in renal cell carcinoma. Two hundred patients with this diagnosis, who were hospitalizd in Oklahoma City an d Tulsa between 1977 and 1980, were matched with 400 controls according to age, sex, race and hospital. Data was collected from hospital records and from questionnaires which were mailed to the living patients, controls (both hospital and general population) and next of kin of the deceased individuals. In addition to the occupational history, other risk factors were analyzed such as family history of cancer, smoking, alcohol consumption, use of hormones, previous illness and radiation therapy. The incidence of renal cell carcinoma was higher than expected in several occupations, including dry cleaners, truck drivers, welders/plumbers and physicians/dentists. There were five dry cleaners among the cases compared to none in the controls. Also 12% of the cases and 5% of the controls responding to the questionnaire were truck drivers. (no Refs)

15. MORTALITY DIFFERENTIAL FOR CANCER BASED ON SOCIAL CLASS: THE METROPOLITAN REGION OF MONTREAL, 1971

Thouez JP

Departement de Geographie, Universite de Montreal, Quebec, Canada.

Soc Sci Med: 18(1):73-81 1984

Cancer mortality rates vary from area to area. Part of this variation is due to socio-economic characteristics of the area and part to other factors including the availability of health services. Three social indicators associated with cancer mortality are used to estimate variations between low and high census sectors within the metropolitan region of Montreal. The components of socio-economic status which have been used are revenue (median family income), education (college and university level) and occupation (higher status profession). For each of the three zones of the metropolitan area: the city of Montreal, the island of Montreal not including the city of Montreal, the north and south shores of the metropolitan area - twenty-five census sectors have been chosen which have higher or lower positions for each of the socio-economic components. For each group standardized death rates were evaluated for each type of cancer and the Poisson test was applied to judge whether the differences between the projected rate and the observed rate were significant. The results indicate a strong indirect relation between the standardized mortality rates and the socio-economic status in the central city. In the case of lung cancer, the spatial distribution showed district gradients of occurrence between the central-city and the suburbs.

16. USE OF THE CANADIAN MORTALITY DATA BASE FOR EPIDEMIOLOGICAL FOLLOW-UP

Smith ME. Newcombe HB

Occupational and Environmental Health Unit, Vital Statistics and Disease Registries Section, Statistics Canada, 17th Floor, R.H. Coats Building, Tunney's Pasture, Ottawa, Ontario, K1A 0Z5, Canada

Can J Public Health: 73(1):39-46 1982

The Canadian Mortality Data Base (CMDB) contains all Canadian death registrations dating from 1950. The CMDB contains personal identifying information, is machine-readable and in microfiche and microfilm form, and is sequenced and consolidated to facilitate manual searching. Several follow-up studies have been performed for various 'at-risk' groups, including infant death-birth linkages, isoniazid and cancer in tuberculosis patients, a 10% sample of the Canadian labor force, and fluoroscopy and cancer in tuberculosis patients. Searches presently in progress involve nickel workers, uranium workers, Ontario workers, particularly miners, Nutrition Canada Survey participants, Ontario morticians, who have high levels of exposure to formaldehyde, railway workers, childbearing women and breast cancer, Alberta cancer files, and fluospar mining in Newfoundland. Several other searches involving the data base are under negotiation, including radiation-exposed workers. The CMDB has the potential for other searches involving individual linear follow-up to investigate health problems associated with diet, food additives, pharmaceuticals, water supply, and workplace conditions. The system is economical and need not threaten personal privacy. (46 Refs)

2.

Studies in Europe and Other Places

17. OCCUPATION AND CANCER IN LONDON: AN INVESTIGATION INTO NASAL AND BLADDER CANCER USING THE CANCER ATLAS

Baxter PJ. McDowall ME

Employment Medical Advisory Service (London N Region), Essex, UK.

Br J Ind Med: 43(1):44-9 1986

The Atlas of Cancer Mortality for England and Wales showed pronounced excesses of male mortality from nasal and bladder cancer in certain London boroughs. These excesses were investigated by case-referent studies using death certificate data for male deaths, 1968-78. Nasal cancer was found to be significantly associated with occupations involving heavy exposure to wood dust. Bladder cancer was significantly associated with occupations in road transport driving and in the handling of leather, whereas consistently raised relative risk ratios were also found for wood-workers, engineering fitters, printers, machinists, plumbers, and motor mechanics. These findings highlight the potential role of occupational factors in cancer causation in London.

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18. SELECTION, FOLLOW-UP, AND ANALYSIS IN THE BIRMINGHAM STUDY

Waterhouse JA
Regional Cancer Registry, Queen Elizabeth Medical Center, Birmingham, United Kingdom.
Natl Cancer Inst Monogr: 67:85-8 1985

The Birmingham, England, Cancer Registry is so organized that every case of cancer in its territory of 5,200,000 persons is included. This coverage allows the staff to detail every epidemiologic aspect of the cancer experience of a whole population. For example, this registry system made it possible for us not only to demonstrate that the Birmingham region had four times the incidence of scrotal cancer as another region had but to identify the locations and the specific practices in the workplac e responsible for the excess. The result was the successful adoption of protective measures. Other instances are presented of the inestimable value of a population-based registry to cancer epidemiology.

19. USE OF JOB-EXPOSURE MATRIX IN AN OCCUPATIONAL ANALYSIS OF LUNG AND BLADDER CANCERS ON THE BASIS OF DEATH CERTIFICATES

Cogwon D, Pannett B, Acheson ED
Environmental Epidemiology Unit, Medical Research Council, University of Southampton, England
JNCI: 72(1):61-5 1984

A job-exposure matrix has been applied in a case-control study of lung and bladder cancer on the basis of occupational information abstracted from British death certificates. The expected association between lung cancer and jobs entailing exposure to asbestos was clearly demonstrated (relative risk, 1.5; 95% confidence interval, 1.2-1.9). The effects of three other known industrial carcinogens were not apparent, and reasons for this were discussed. Also included in the matrix were five substances whose carcinogenicity in humans has not been established. Formaldehyde, diesel fumes, and cutting oils were all associated with carcinoma of the bronchus, but the absence of a risk in 'high-exposure' occupations was against a causal relationship. Bladder cancer was more common in jobs involving high exposure to printing inks (relative risk, 5.0; 95% confidence interval, 1.0-25.8) and cutting oils (relative risk, 1.5; 95% confidence interval, 0.8-2.8). Use of the job-exposure matrix added considerably to the conventional analysis of cancer risk in individual occupational categories.

20. VARIATIONS IN CANCER MORTALITY AMONG LOCAL AUTHORITY AREAS IN ENGLAND AND WALES: RELATIONS WITH ENVIRONMENTAL FACTORS AND SEARCH FOR CAUSES

Gardner MJ, Winter PD, Acheson ED
Medical Res. Council's Environmental Epidemiology Unit, Univ. Southampton, Southampton General Hosp., Southampton SO9 4XY, England
Br Med J: 284(6318):784-787 1982

Geographical variations in specific causes of mortality among the 1366 local authority areas of England and Wales as defined in 1971 were studied by examining extracts from death certificates held on computer tape. Five items of information on each death (yr of death, age at death, sex, local authority area of residence, and the underlying cause of death, during the 11 yr 1968-78) permitted a more detailed investigation than had been possible before. Analysis of some early results of the study (including maps of mortality for pleural mesothelioma, nasal cancer, and bladder cancer) suggested that, despite the known limitations of death certification, systematic study of the mortality of small areas may give clues to etiological factors in the environment. Analyses relating mortality to the distribution of environmental factors and examining disease profiles of each area may also provide clues. These will be followed up by other methods of study, such as case-control techniques. (Author abstract) (20 Refs)

21. EPIDEMIOLOGY OF BLADDER CANCER

Bouffioux CR
Urological Department, Hopital de Bariere, University of Liege, Belgium.
Prog Clin Biol Res: 162A:11-25 1984

Keywords (MeSH): Age Factors; Amines/adverse effects; Antineoplastic Agents/adverse effects; Belgium; Bladder Neoplasms/chemically induced/etiology/*occurrence; Carcinogens, Environmental/adverse effects; Carcinoma, Transitional Cell/*occurrence; Coffee/adverse effects; Cyclophosphamide/adverse effects; Diet; Europe; Human; Japan; Neoplasms, Radiation-Induced/etiology; Occupational Diseases/chemically induced; Phenacetin/adverse effects; Risk; Smoking; Sweetening Agents/adverse effects; United States; Urinary Tract Infections/complications.

22. HIGH MORTALITY CAUSED BY UROTHELIAL CANCER AND OCCUPATIONAL EXPOSURE. A STUDY OF PROPORTIONAL MORTALITY

Villalbi JR, Costa-Ribot J, Canela J
Actas Urol Esp: 8(4):297-300 1984

Keywords (MeSH): Adolescence; Adult; Aged; Blauder Neoplasms/*mortality; Chemical Industry; Child; Child, Preschool; English Abstract; Female; Human; Infant; Infant, Newborn; Male; Middle Age; Occupational Diseases/*mortality; Spain.

23. OCCUPATION, TOBACCO USE, COFFEE, AND BLADDER CANCER IN THE COUNTY OF MATARO (SPAIN)

Gonzalez CA, Lopez-Abente G, Errezola M, Castejon J, Estrada A, Garcia-Mila M, Gili P, Huguet M, Serrat M, Soler F, et al
Unit of Epidemiology and Biostatistics, Hospital of Mataro, Barcelona, Spain.
Cancer: 55(9):2031-4 1985

This report presents the results of an epidemiologic case-control study. The study includes 58 cases and 116 controls from both sexes, selected from the Admission Register of the Hospital and from the Death Registry Office of the local city authorities. Controls have been matched to cases by age, sex, place of residence and source of selection. The results demonstrated no increased risk associated with coffee consumption. Habitual smokers present a 2.3 times higher risk than nonsmokers. The estimated relative risk for occupation standardized by age and smoking habit, is 5.5. A multiplicative effect of the simultaneous action of smoking and occupational exposure has been observed to be an estimated relative risk of 11.7. The attributable risk of the population has been estimated to be 39% for smokers and 12% for occupational exposure. A strong association was found between bladder cancer and occupational exposure to carcinogenic substances, especially in the dye and print textile industries.

24. OCCUPATION AND BLADDER CANCER IN MALES: A CASE-CONTROL STUDY

Vineis P, Magnani C
Unit of Cancer Epidemiology, Main Hospital, Turin, Italy.
Int J Cancer: 35(5):599-606 1985

A case-control study of 512 male cases of bladder cancer and 596 male hospital controls (all living in the province of Turin, Northern Italy, an area with a high proportion of car workers) has been an alyzed for occupations. Relative risks were 1.8 (95% c.l. 0.9-3.6) for the textile industry, 3.8 (1.3-

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11.5) for the leather industry, 1.8 (0.8-4.0) for printing, 8.8 (2.7-28.6) for dyestuff production, 1.2 (0.6-2.4) for tire production and 2.5 (1.0-6.0) for other rubber goods, 2.0 (0.9-4.5) for brickyards and related activities. A relative risk of 3.1 (0.9-10.5) was found for turners having started work before 1940 and with at least 10 years of activity. For truck drivers the relative risk was 1.2 (0.6-2.5). A job-exposure matrix was developed for the development of new hypotheses; an association with bladder cancer was found for aromatic amines only. The attributable risk percent in the population was estimated as 10%, when only those occupations consistently associated with bladder cancer were considered.

25. ESTIMATES OF THE PROPORTION OF BLADDER CANCERS ATTRIBUTABLE TO OCCUPATION

Vineis P, Simonato L
Unit of Cancer Epidemiology, Main Hospital, Turin, Italy.
Scand J Work Environ Health; 12(1):55-60 1986

In order to estimate the proportion of bladder cancers attributable to occupation in different countries, three criteria were defined, each with a different degree of strictness, for the inclusion of job titles or industrial activities in the estimates. Such criteria were applied to the available case-referent studies, the range for the less severe criterion estimates being 0-19% and that of the strictest being 1-19%. The variability was greater among the studies than among the criteria of inclusion of occupations; therefore the study design and time- and place-specificity of exposures play an important role in the magnitude of such estimates.

26. OCCUPATIONAL EXPOSURES AS RISK INDICATOR OF MALE BLADDER CARCINOMA IN A PREDOMINANTLY RURAL AREA

Mommsen S, Aagard J
Department of Oncology and Radiotherapy, University of Aarhus, Denmark.
Acta Radiol Oncol; 23(2-3):147-52 1984

A case-control study was performed on 212 bladder carcinoma patients (165 men and 47 women) and 259 control persons (165 men and 94 women) matched according to age and geographical area. Bivariate associations among the males revealed an increased relative risk (RR) of developing bladder carcinoma associated with occupational exposure to oil or gasoline, chemical materials, kerosene or asphalt. A significantly increased RR of developing bladder carcinoma was associated with blacksmiths and mechanics. A logistic regression analysis did not reveal an independent statistical effect of this parameter. Among the occupational factors, exposure to oil or gasoline was the most informative aetiologic determinant.

27. EPIDEMIOLOGY OF BLADDER CANCERS

Pastel P, Schaffer P, Bollack C
Registre des cancers du Bas-Rhin, Faculte de medecine, Strasbourg.
J Urol (Paris); 91(6):323-8 1985

Keywords (MeSH): Aged; Bladder Neoplasms/etiology/mortality/*occurrence; Caffeine/adverse effects; Carcinogens; Comparative Study; Female; France; Human; Male; Middle Age; Neoplasms, Radiation-Induced; Occupational Diseases/occurrence; Registries; Risk; Rural Population; Saccharin/adverse effects; Schistosomiasis Haematobia; Tobacco; Urban Population.

28. CLINICAL STUDY ON OCCUPATIONAL UROEPITHELIAL CANCER IN WAKAYAMA CITY

Obkawa T, Fujinaga T, Doi J, Ebisuno S, Takamatsu M, Nakamura J, Kido R
Dept. Urology, Biochemistry, Wakayama Medical Coll., Wakayama, Japan
J Urol; 128(3):520-523 1982

There were 64 confirmed cases of occupational uroepithelial cancer in Wakayama City, Japan. The annual morbidity per 100,000 exposed persons was 198.3. The latent period ranged from 5 to 45 years, with an average of 21.1 plus or minus 9.8 years (standard deviation). The latent period tended to be shorter as age advanced. Cytological examinations were useful for early discovery of occupational uroepithelial cancer. (Author abstract) (10 Refs)

29. [DOUBLE CANCER OBSERVED IN OCCUPATIONAL AND ENVIRONMENTAL BLADDER CANCER]

Matsushima M, Yagishita T, Fukasawa K, Tajima M, Miura K, Kawahara M, Sawamura Y, Miyamae K, Ando K
Nippon Hinyokika Gakkai Zasshi; 75(8):1306-18 1984

Keywords (MeSH): Adult; Aged; Bladder Neoplasms/occurrence; Carcinoma, Transitional Cell/*occurrence; Dyes/adverse effects; English Abstract; Female; Human; Male; Middle Age; Neoplasms, Multiple Primary/*occurrence; Occupational Diseases/*occurrence; Smoking; Urologic Neoplasms/*occurrence.

30. THE CLINICIAN AND EPIDEMIOLOGY FOR CANCER RESEARCH

Yoshida O
Dept. of Urology, Fac. of Medicine, Kyoto University, Japan.
Sangyo Ika Daigaku Zasshi; 5 Suppl:203-6 1983

Keywords (MeSH): Azo Compounds; Bladder Neoplasms/chemically induced; Case Report; Dyes; Epidemiologic Methods; Human; Japan; Male; Middle Age; Neoplasms/*occurrence; Occupational Diseases/chemically induced/*occurrence; Prostatic Neoplasms/occurrence.

B.

Urinary Tract or Prostate Cancer Due to Occupational Exposure to Specific Chemicals

1.

Occupational Exposure to Aromatic Amines

31. BLADDER TUMOR INCIDENCE AMONG WORKERS EXPOSED TO BENZIDINE: A THIRTY-YEAR FOLLOW-UP

Meigs JW, Marrett LD, Ulrich FU, Flannery JT
Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06510.
JNCI; 76(1):1-8 1986

Linkage with records of the Connecticut Tumor Registry was used to determine cancer incidence in a cohort of workers (n = 984) at a benzidine manufacturing facility. Compared to the findings for the Connecticut population, there was a statistically significant excess of bladder tumor among male cohort members [standardized incidence ratio (SIR) = 343; 95% confidence limits (CL) = 148, 676; n = 830], which was confined to those with the highest estimated level of benzidine exposure (SIR = 1,303; CL = 479, 2,839; n = 105). No significantly elevated risks were found for cancers at other anatomic sites in men or at any anatomic sites in women; nor was there any pattern of increasing risk with increasing benzidine exposure for sites other than bladder. In addition, the elevated bladder cancer risk was greater for men first employed during the earliest years of the plant, namely, 1945-49

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(SIR = 976; CL = 262, 2,498) as compared to those first employed in 1950-54 (SIR = 213; CL = 3, 1,184) after equalization of duration of follow-up. These results suggest that the major preventive measures instituted around 1950 may have reduced bladder cancer risk in this plant.

32. NOTIFICATION AND RISK ASSESSMENT FOR BLADDER CANCER OF A COHORT EXPOSED TO AROMATIC AMINES. III. MORTALITY AMONG WORKERS EXPOSED TO AROMATIC AMINES IN THE LAST BETA-NAPHTHYLAMINE MANUFACTURING FACILITY IN THE UNITED STATES

Stern FB, Murthy LI, Beaumont JJ, Schulte PA, Halperin WE
National Institute for Occupational Safety and Health, Robert A Taft Laboratories, Cincinnati, OH 45226.
J Occup Med; 27(7):495-500 1985

A retrospective cohort mortality study was conducted among workers employed at the last facility in the United States that manufactured beta-naphthylamine (BNA), a recognized human bladder carcinogen. This study was conducted in conjunction with a pilot project in which workers were notified of the health risks associated with exposures to carcinogenic amines. Cause-specific mortality for 1,312 male workers employed between 1940 and 1972, and followed through 1979, was compared with the mortality of the general population in the United States. Two deaths from bladder cancer were observed while 0.7 such deaths were expected. Due to the use of these potent carcinogenic amines, it had been anticipated that more bladder cancer deaths would be found in this population. The reasons for the small number of bladder cancer deaths could have been the low percentage of the work force exposed, an inadequate latency period, and/or the high survival rate for bladder cancer. In fact, a notification and medical screening project recently conducted in this same population found an additional 11 bladder cancer cases. This suggests that mortality may not always be an adequate indicator of disease risk.

33. RISK ASSESSMENT OF A COHORT EXPOSED TO AROMATIC AMINES. INITIAL RESULTS

Schulte PA, Ringen K, Hemstreet GP, Altekruse EB, Gullen WH, Patton MG, Allsbrook WC Jr, Crosby JH, West SS, Witherington R, et al
National Institute for Occupational Safety and Health, Cincinnati, OH
J Occup Med; 27(2):115-21 1985

A cohort of 1,385 workers potentially exposed to carcinogenic amines was evaluated to determine the extent of its risk for bladder cancer. The cumulative incidence of bladder cancer was determined from death certificates, from interviews with community urologists, and from a screening program. A total of 13 confirmed cases of bladder cancer were identified at the conclusion of the first year of study. The entire cohort has approximately a fourfold excess risk of bladder cancer; however, black workers with more than 10 years of employment had a risk ratio of 111 (based on three cases). The onset of disease occurred, on the average, 15 years earlier in these black workers than in the general U.S. population. The cumulative incidence of bladder cancer increased with the duration of employment, ranging from 0.4% for workers with five or fewer years of employment to 36% for those with greater than 20 years. No significant differences were found between cases and noncases for cigarette smoking, coffee drinking, use of artificial sweeteners, or prior employment in high-risk occupations. More cases of bladder cancer are expected in this cohort because many members have not yet achieved the average latency found for the confirmed cases. (19 Refs)

34. BLADDER CANCER MORTALITY OF WORKERS EXPOSED TO AROMATIC AMINES: ANALYSIS OF MODELS OF CARCINOGENESIS

Decarli A, Peto J, Piolatto G, La Vecchia C
Institute of Medical Statistics, University of Milan, Italy
Br J Cancer; 51(5):707-12 1985

The effects of various factors were evaluated on both relative risk (multiplicative model), and absolute excess risk (additive model) of bladder cancer among 664 workers of a dyestuff factory in Northern Italy. These workers were exposed to aromatic amines in fairly constant working conditions from 1922 to 1970, and were employed for at least one year. They were followed up till the end of 1981 for a total of 12,302 man-years at risk. Under both models, the risk was greater for workers directly involved in aromatic amine manufacture than for those with only intermittent exposure. There was no marked effect of age at first exposure on the absolute excess risk of bladder cancer, but the relative risk was strongly and negatively related to age at first exposure. Under the multistage theory of carcinogenesis, this pattern of risk indicates an early stage effect. Absolute excess risk increased sharply during exposure, and continued to rise, although less sharply, after exposure had ceased. Relative risk, however, decreased after cessation of exposure, indicating a possible late stage effect. Thus, the results derived from both additive and multiplicative models are not in contrast when interpreted in terms of the multistage theory of carcinogenesis, though they are not totally consistent with a single-stage effect, either early or late. Aromatic amines may act on a stage somewhere between the first and penultimate, or on more than one stage of the process of carcinogenesis. Alternatively, it is possible that imprecision in the job classification or other observational problems may obscure the trends, or produce fictitious trends in the effects of variables such as age at first exposure and time since last exposure. Finally, such a pattern of trends could emerge if there were only two stages and the first and penultimate stage were the same.

35. BLADDER CANCER IN DYE MANUFACTURING WORKERS

Boyko RW, Carturight RA, Glashen RW
Department of Community Medicine, University of Leeds, England.
J Occup Med; 27(11):799-803 1985

Results of an occupational analysis of chemical dye workers, using data from a larger case-control study of bladder cancer in West Yorkshire, England, are presented. The current nature of the risk of bladder cancer experienced by such workers is assessed on an unmatched case-control basis. The results indicate that the bladder cancer risk has peaked for workers exposed to arylamines, but that they still experience a twofold to threefold increased risk even after adjustments for age and smoking. A dose-response relationship is demonstrated, linked to the number of years of occupational exposure. However, results obtained under stratification, commensurate with the dates of introducing revised working practices, indicate that the calendar years during which exposure occurred are more important, in relation to increased bladder cancer risk, than is length of exposure.

36. EPIDEMIOLOGY OF AROMATIC AMINE CANCERS

Parkes HG, Evans AE
British Rubber Manufacturers' Association Ltd., Scala House, Holloway Circus, Birmingham B1 1EQ England
ACS Monogr; (182):277-301 1984

The toxicity of the aromatic amines, which is closely linked with the toxicity of the related nitro compounds, has been recognized since the early industrial use of aniline, when the clinical picture of 'anilism' was first seen. Cystitis, hematuria,

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methemoglobinemia, and dermatitis were the principal manifestations of this toxicity, but the problem of such symptoms and signs was in most cases speedily resolved by improved manufacturing practices. Although industrial exposure to aromatic amines has been linked to occupational bladder cancer since the end of the last century, the present understanding of the problem dates from epidemiological studies of Case et al. In vitro and in vivo testing has now shown conclusively tha: many aromatic amines have the potential to cause cancer; therefore vigilance must be maintained to ensure that the currently accepted 'nonindustrial' tumors are not due to unrecognized industrial exposure. Current toxicological screens may enable industry to filter out some of the potential human carcinogens, but complete success is an ideal that will remain unrealized irrespective of the extent and complexity of the screening protocol. Nevertheless, the availability and the successful application of epidemiological techniques in the identification of occupational cancer hazards may contribute significantly in the future to the ability to monitor and thus diminish the risk of human exposure to potential carcinogens. The epidemiology of the aromatic amine cancers is discussed under the following headings: aromatic amines of industrial importance, epidemio logy of bladder cancer, industrial bladder cancer, epidemiology of industrial bladder cancer, the work of R.A.M. Case, screening, compensation, legal liability, and legislation. The epidemiology of the aromatic amine cancers is, for all practical purposes, synonymous with the epidemiology of industrial bladder cancer. A victim of industrial bladder cancer cannot be adequately compensated for the infliction of an injury that will in many cases cost him his life. The influence that government action by legislation may have on the manufacture and use of carcinogenic or suspect carcinogenic materials is considered. (90 Refs)

37. A MORTALITY SURVEY OF MEN ENGAGED IN THE MANUFACTURE OF ORGANIC DYES

Ott MG. Langner RR

Health and Environmental Sciences. Dou Chemical Company. Midland. MI.

J Occup Med: 25(10):763-8 1983

The mortality experience of 342 employees assigned to three aromatic amine-based dye production areas was examined in relation to duration of employment and interval since entry into these areas. No deaths due to bladder cancer were observed, and no statistically significant increases in mortality by work area or duration of exposure within work area were found, based on comparison with the mortality experience of the U.S. white male population. There were incidental findings of more digestive malignancies than expected in one production area, and more digestive and respiratory malignancies than expected in a second area; none of these were statistically significant. Because the digestive malignancies were not site-specific, and because similarities in specific job assignments were lacking for both digestive and respiratory malignancies, it is unlikely that these findings were work related. Nonetheless, in subsequent assessments of the present cohort and other populations exposed to similar materials an effort should be made to evaluate the occurrence of digestive and respiratory malignancies.

38. MONITORING OF LABORERS PREVIOUSLY EXPOSED TO AROMATIC AMINES, IN ACCORDANCE WITH CIRCULARS NO. 46 OF 12/6/1979 AND NO. 61 OF 4/6/1981 OF THE MINISTRY OF LABOR

Seghizzi P. Cassina G. Malinverni C. Maconi G. Belotti L. Mustelli O. Ghisi R

Ospedali Riuniti di Bergamo. Istituto di Medicina del Lavoro.

G Ital Med Lav: 5(3):207-13 1983

The present report deal, a year after its beginning, with the results of a programme for health control regarding 592 exemplovees of Societa Bergamasca Industrie Chimiche. Azo dyes were obtained from benzidine and beta-naphthylamine in this factory from 1947 to 1968. The report analyses the organizing difficulties and the troubles which caused a scarce performance of the programme at different levels: the subjects interested in the control, the Commission responsible for the district, the doctors in charge, the laboratories, the hospital division. In the end some proposals are advanced referr ing to the provision of the ministerial circular letter n.o 46, dated june 12, 1979, about the medical control of workers who leave the hazardous working job.

39. AROMATIC AMINES IN THE WORK ENVIRONMENT AND UROTHELIAL TUMORS

Conso F

Hopital Raymond-Poincare. Faculte Paris-Ouest. Garches.

Sem Hop Paris: 59(29-30):2103-6 1983

According to existing cancerology registers, 6500 new cases of cancer of the bladder are diagnosed and treated each year in males in France (and 1800 in females). Less than ten or so of these are considered as occupational diseases, whereas in European countries with similar industrial development 5 to 10% of carcinomas of the bladder are ascribed to an occupational exposure or a carcinogen. There are several reasons why the occupational origin of these tumors often escapes recognition in our country in spite of adequate professional medical monitoring: the usually long time interval - averaging 20 years - between exposure to the carcinogen and apparition of the tumor; difficulties in eliciting the complete occupational history and in ascertaining, within this history, a possible contaminating exposure; the restrictive nature of the current list of occupational diseases which includes only carcinogens that have been known for many years; the possible interaction between several carcinogenic factors, especially involving tobacco. General practitioners must be made aware of the necessity of investigating the occupational history of patients with bladder cancer who are no longer followed-up by industrial doctors. The main risks are found in chemical industries, particularly the dye industry, textile industries, rubber industries, laboratory occupations and handling of raticides.

40. HISTORICAL AND MODERN EPIDEMIOLOGICAL STUDIES ON POPULATIONS EXPOSED TO N-SUBSTITUTED ARYL COMPOUNDS

Carturight RA

Yorkshire Regional Cancer Organisation. Cookridge Hosp.. Leeds 16. England

Environ Health Perspect: 49:13-19 1983

The historical exposures to aromatic amines of various occupational groups are briefly reviewed. Modern studies indicate that other occupational groups might have risks worth investigating; these include machinists and workers in the chemical industry. Details of a recent investigation into the exposure of dye workers are given which indicate a lowered risk in recent years since the introduction of safety measures. Nonoccupational exposures to the aromatic amines are also discussed. They include cigarette smoking and phenacetin

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abuse, the former being a potent causal agent in bladder cancer. (Author abstract) (34 Refs)

41. MULTIPLE PRIMARY CANCERS FOLLOWING EXPOSURE TO BENZIDINE AND BETA-NAPHTHYLAMINE

Morinaga K. Oshima A. Hara I
Dept. Field Res., Center for Adult Diseases, Osaka, 3 Nakamichi 1-chome, Higashinari-ku, Osaka 537, Japan
Am J Industr Med: 3(3):243-246 1982

The incidence of second primary cancers was determined in 3,322 workers involved in the manufacture of benzidine and beta-naphthylamine from 1950-1978. Among these workers, 244 developed cancer and subsequently died of cancer of the genitourinary organs. Subsequent histologically confirmed primary cancers developed in 11 cases, all males; ages at time of diagnosis ranged from 35-67 yr while latent periods ranged from 8-27 yr. The first primary cancers in the 11 cases were all transitional cell carcinomas, 9 of the bladder and 1 each of ureter and renal pelvis. The second primary cancers included 1 squamous cell carcinoma (maxillary sinus) and 10 adenocarcinomas (lung 3, prostate 2, and 1 each adrenal cortex, liver, bile duct, rectum, gallbladder, and colon). Interval between diagnosis of the first and second primary cancers ranged from 4 mo-14 yr (av 5.7 yr). A control group of 177 male bladder cancer patients (from the Osaka Cancer Registry) showed 8 cases of a second primary, 5 of which were of the stomach. The exposed group showed a statistically significant excess of risk for liver, gallbladder, and bile duct cancer (p less than 0.05). While it is possible that those in the exposed group smoked more than the controls, the fact that all three lung cancers were adenocarcinomas suggests that the aromatic amines may have been responsible. (5 Refs)

42. THE CARCINOGENIC EFFECT OF AROMATIC AMINES: AN EPIDEMIOLOGICAL STUDY ON THE ROLE OF O-TOLUIDINE AND 4,4'-METHYLENE BIS(2-METHYLANILINE) IN INDUCING BLADDER CANCER IN MAN

Rubino GF. Scansetti G. Piolatto G. Pira E
Inst. Occupational Health, Turin Univ., CTO- Via Zuretti, 29-10126 Torino, Italy
Environ Res: 27(2):241-254 1982

Cause-specific mortality of 906 workers first employed 1922-1970 in a dyestuff factory in Northern Italy was compared to national figures; a marked excess of bladder cancer was observed (36 observed vs 1.23 expected deaths). The mean latent period was 25 years. The excess was higher among those with longer duration of exposure. Some excess of mortality from lung cancer, laryngeal cancer, and esophageal cancer was also found, but a clear explanation could not be provided regarding the causal role of aromatic amines. Mortality from bladder cancer was very much higher among those exposed in benzidine and naphthylamines manufacture as compared to those only exposed in use or intermittent contact. Excess bladder cancer was also very high among workers in fuchsin manufacture. There is evidence that O-toluidine and 4,4'-methylene bis(2-methylaniline) should be implicated in such excess mortality. Caution in handling these compounds is therefore suggested and the need for further studies to confirm such findings is stressed. (Author abstract) (19 Refs)

43. AMINE TUMORS OF THE BLADDER. POSSIBLE ROLE OF INDUSTRIAL EXPOSURE TO O-TOLUIDINE AND O-AMINOAZOTOLUE NE

Conso F. Pontal P
Hopital Raymond-Poincare, 92380 Garches, France
Arch Mal Prof: 43(4):307-310 1982

Epidemiological studies of the relationship of O-toluidine (OT) and O-aminoazotoluene (OAAT) to bladder cancer are described. In a study of factory workers exposed to aromatic amines, bladder cancer was detected in 3/56 men. Problems associated with studying the role of OT and OAAT in bladder cancer are the relatively short latency period and the short duration of exposure required. It is important for physicians in occupational medicine to determine the real danger associated with chemicals handled, to detect urothelial lesions as early as possible, and to determine genetic predispositions in certain individuals. (17 Refs)

44. PERIODIC URINE CYTOLOGY SURVEILLANCE OF BLADDER TUMOR INCIDENCE IN DYESTUFF WORKERS

Yamaguchi N. Tazaki H. Okubo T. Toyama T
35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
Am J Industr Med: 3(2):139-148 1982

Nine cases of urinary bladder tumors in workers who had been exposed for various lengths of time to benzidine (BZ) and beta-naphthylamine (BNA) were reviewed in order to evaluate the validity of urine cytology surveillance of occupational bladder tumor incidence. The patients were all men, and ranged in age from 40 to 66 yr. Six patients had been followed up with periodic urine cytological checks and three had not; cytological checks detected neoplasms in 5/6 of the cases. One of the patients whose neoplasm was not detected by cytology died 9 yr after his first operation and one of the monitored patients also died, 11 yr after first operation; the other seven patients are alive and healthy. Five patients whose cases were detected by gross hematuria underwent partial or total cystectomy, whereas the remaining four cases whose tumors were detected by urine cytology only required transurethral operation. The av time interval between the first exposure to BZ or BNA and detection of tumor was 26.4 +-6.0 yr; the interval between the last exposure and detection of tumors was 14.0 +-6.2 yr. Urine cytology was apparently effective in detecting bladder tumors, but the long latent periods for BZ and BNA exposure indicate that long follow-up periods are necessary. (12 Refs)

45. ARYLAMINES AND BLADDER CANCER CAUSALITY: APPLICATION OF CONCEPTUAL AND OPERATIONAL CRITERIA

Lower GM Jr
Institute for Environmental Studies, University of Wisconsin, Madison.
Clin Pharmacol Ther: 34(2):129-35 1983

Keywords (MeSH): Acetylation; Amines/*adverse effects; Bladder Neoplasms/*chemically induced/familial and genetic; Environmental Exposure; Human; Occupational Diseases/chemically induced; Phenotype; Smoking.

46. OCCUPATIONAL CANCER OF THE URINARY BLADDER: THE DIAGNOSTIC VALUE OF URINARY CYTOLOGY IN DYESTUFF WORKERS EXPOSED TO AROMATIC AMINE

Matsushima M. Murakami N. Fukazawa K. Yagishita T. Fujio K. Miura K. Sawamura Y. Tajima M. Nakayama K. Shirai M. Ando K
Nippon Hinyokika Gakkai Zasshi: 74(1):81-99 1983

Keywords (MeSH): Adult; Amines/*adverse effects; Bladder Neoplasms/chemically induced/*occurrence; Carcinoma,

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Transitional Cell/chemically induced/*occurrence; Case Report; Cytodiagnosis; Dyes/adverse effects; English Abstract; Human; Male; Mass Screening/*methods; Middle Age; Occupational Diseases/chemically induced/*occurrence; Time Factors; Urine/*cytology.

2.

Occupational Exposure to Chrysoidine Azo Dyes

47. COARSE FISHING AND RISK OF UROTHELIAL CANCER

Sole G. Sorahan T
Department of Urology, Queen Elizabeth Hospital, Birmingham.
Lancet: 1(8444):1477-9 1985

In a case-control study of 240 men with urothelial cancer diagnosed in 1984 and 240 matched control subjects smoking and coarse fishing were found to be significantly associated with the disease. Duration of exposure to the chrysoidine azo dyes used to stain maggot bait was the most important predictor of risk; 5% of our cases were attributable to exposure to this dye. Chrysoidine dyes are chemically similar to some putative mammaliar carcinogens and a constituent of hair dyes.

48. DOES THE USE OF STAINED MAGGOTS PRESENT A RISK OF BLADDER CANCER TO COARSE FISHERMEN?

Cartwright RA, Robinson MR, Glashan RW, Gray BK, Hamilton-Stewart P, Cartwright SC, Barham-Hall D
Yorkshire Regional Cancer Organisation, Cookridge Hosp., Leeds 16, England
Carcinogenesis: 4(1):111-113 1983

A case-control study in West Yorkshire has been used to investigate possible risks of bladder cancer among those fishermen who used azo-based dyestuffs to stain maggots or who purchased ready colored maggots. No risks have been found, although the confidence limits of the estimates are wide. These data refer to exposures over 10 yr ago and it is possible recent changes in fishing practice, if they have occurred, are not yet assessable due to the long mean latency seen in bladder cancer when exposure to carcinogens is not great. This paper does not suggest the general use of these substances is without hazard, merely that no risk is associated with the study group and that the chemicals under study are not a major cause of bladder cancer. (Author abstract) (8 Refs)

49. IS DYEING OF BAIT A CARCINOGENIC HAZARD FOR ANGLERS AND THEIR SUPPLIERS? (MEETING ABSTRACT)

Searle CE, Teale J
Department of Cancer Studies, The Medical School, Birmingham B15 2TJ, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Chrysoidine (2,4-diaminoazobenzene), once used as a food dye, induced liver tumors in most male and female mice when fed at 0.2% in the diet, and it was the most active of some azo dyes and reduction products tested for mutagenicity in Salmonella typhimurium TA 1538. Nevertheless it is currently in widespread use for dyeing maggots for use as bait by anglers, for which purpose the hydrochloride is mixed with maggots by anglers' suppliers shortly before sale. This causes considerable long-lasting staining of the hands of shop staff and, to a lesser extent, of the very many anglers who use the bait, often from an early age. A Midlands dealer, who uses 14 kg of chrysoidine HCl annually, became anxious about its safety and informed us of 3 angling acquaintances who had developed bladder tumors. The early ages of presentation -2 were under 40-would suggest a possible 'occupational' origin, but none had worked in the chemical or rubber industries. Some other dyes, including the carcinogen auramine, have also been used but apparently with lesser problems of contamination. (2 Refs)

50. A CATCH EVERY TIME

Anonymous
Food Chem Toxicol: 21(5):690 1983

Keywords (MeSH): Animal; Bladder Neoplasms/*chemically induced; Dyes/*adverse effects; Fishes; Human; Occupational Diseases/*chemically induced.

3.

Occupational Exposure to Cadmium

51. PROSTATIC CANCER AND CHRONIC RESPIRATORY AND RENAL DISEASE IN BRITISH CADMIUM WORKERS: A CASE CONTROL STUDY

Armstrong BG, Kazantzis G
TUC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, UK.
Br J Ind Med: 42(8):540-5 1985

Deaths due to prostatic cancer, renal cancer, bronchitis or emphysema, and nephritis or nephrosis in three cohorts of cadmium workers have been investigated in a case-control study. Evidence of an association of risk for these diseases with intensity and duration of exposure to cadmium was sought. The only clearly statistically significant finding was of an association of deaths coded as bronchitis or emphysema with 'high' levels of exposure to cadmium fume, which was related also to duration of exposure. There was suggestive evidence also (p congruent to 0.10) of an increased risk for nephritis or nephrosis after high exposure. Marginally increased risks were observed for prostatic cancer after high or 'medium' exposure, but these were not statistically significant.

52. CANCER MORTALITY OF CADMIUM WORKERS

Elinder CG, Kjellstrom T, Hogstedt C, Andersson K, Spang G
Department of Occupational Medicine, National Board of Occupational Safety and Health, Solna, Sweden.
Br J Ind Med: 42(10):651-5 1985

Several epidemiological studies of workers exposed to cadmium indicate an increased risk of lung and prostatic cancer. The increase is statistically significant in some of the studies but the SMR is greater than 100 in almost all. A cohort study of the mortality among 522 Swedish workers exposed to cadmium for at least one year in a nickel-cadmium battery plant support the earlier findings. The SMR for lung and prostatic cancer increased with increasing dose and latency but did not obtain statistical significance. A combination of all the available data from the most recent follow up of causes of death among cadmium workers in six different cohorts shows 28 cases of prostatic cancer (SMR = 162) and 195 cases of lung cancer (SMR = 121). This new analysis suggests that long term, high level exposure to cadmium is associated with an increased risk of cancer. The role of concomitant exposure to nickel needs further study.

53. HUMAN HEALTH EFFECTS OF EXPOSURE TO CADMIUM

Hallenbeck WH
School of Public Health, University of Illinois at Chicago.
Experientia: 40(2):136-42 1984

The health effects of human exposure to cadmium are discussed with emphasis on intake, absorption, body burden,

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and excretion; osteomalacia in Japan; hypertension; and proteinuria, emphysema, osteomalacia, and cancer in workers. Elevated blood pressure has not been observed as a result of excessive exposures to cadmium in Japan or the workplace. Renal tubular dysfunction and consequent proteinuria is generally accepted as the main effect following long-term, low-level exposure to cadmium. Studies of workers show that proteinuria may develop after the first year of exposure or many years after the last exposure. Proteinuria and deterioration of renal function may continue even after cessation of exposure. The immediate health significance of low level proteinuria is still under debate. However, there is evidence that long-term renal tubular dysfunction may lead to abnormalities of calcium metabolism and osteomalacia. The few autopsy and cross-sectional studies of workers do not permit conclusions to be drawn regarding the relationship between cadmium exposure and emphysema. Retrospective and historical-prospective studies are needed to settle this important question. No conclusive evidence has been published regarding cadmium-induced cancer in humans. However, there is sufficient evidence to regard cadmium as a suspect renal and prostate carcinogen. Because of equivocal results and the absence of dose-response relationships, the studies reviewed should be used with caution in making regulatory decisions and low-dose risk assessments. (62 Refs)

54. MORTALITY STUDY OF NICKEL-CADMIUM BATTERY WORKERS BY THE METHOD OF REGRESSION MODELS IN LIFE TABLES

Sorahan T. Waterhouse JA
Cancer Epidemiology Research Unit, University of Birmingham, Edgbaston, UK
Br J Ind Med 40(3):293-300 1983

The mortality experienced by a cohort of 3025 nickel-cadmium battery workers during the period 1946-81 has been investigated. Occupational histories were described in terms of some 75 jobs: eight with 'high', 14 with 'moderate' or slight, and 53 with minimal exposure to cadmium oxide (hydroxide). The method of regression models in life tables (RMLT) was used to compare the estimated cadmium exposures (durations of exposed employment) of those dying from causes of interest with those of matching survivors in the same year of follow up, while controlling for sex, for year and age of starting employment, and for duration of employment. No new evidence of any association between occupational exposure to cadmium oxide (hydroxide) and cancer of the prostate was found.

55. CANCER OF PROSTATE AMONG NICKEL-CADMIUM BATTERY WORKERS [LETTER]

Sorahan T. Waterhouse JA
Lancet. 1(8426):459 1985

Keywords (MeSH): Cadmium/*adverse effects; Human; Male; Nickel/*adverse effects; Occupational Diseases/*etiology; Prostatic Neoplasms/*chemically induced.

4.
Occupational Exposure to Nickel

56. SITE-SPECIFIC CANCER MORTALITY AMONG WORKERS INVOLVED IN THE PRODUCTION OF HIGH NICKEL ALLOYS

Redmond CK
Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh.
IARC Sci Publ: 53:73-86 1984

This report describes the cause-specific mortality patterns of 28 261 workers employed at 12 plants involved in the production of high nickel alloys during the late 1950s and 1960s and followed up to 31 December 1977. Findings for site-specific cancers that have previously been related to nickel exposures are: (1) Overall, no statistically significant increased risk has been observed for cancers of the lung, nasal sinuses, larynx or kidney. (2) When data were examined by occupational groupings, an excess risk of dying from cancers of the lung of about 25-50% for males employed in maintenance categories has been noted. It is unclear whether the greater risk is directly associated with nickel exposures, particularly since a similar excess is not found in other occupational groups where nickel exposures are also present. Two other cancer sites, liver and large intestine, not previously associated with nickel exposures in epidemiological studies, demonstrate a statistically significant standardized mortality ratio (SMR). The SMRs are 182 and 233 respectively, and observed increases in SMRs are found primarily among longer-term workers in the industry but are not concentrated in a particular work area or occupational category. No conclusion regarding a causal association with nickel has been drawn for these two sites at this time.

57. CANCER INCIDENCE AT A HYDROMETALLURGICAL NICKEL REFINERY

Egedahl R. Rae E
Department of Community Medicine, Faculty of Medicine, University of Alberta, Edmonton, Canada
IARC Sci Publ: 53:47-55 1984

Sherritt Gordon Mines Limited established hydrometallurgical nickel refining operations at Fort Saskatchewan, Alberta, in 1954. Records of workers with a minimum of one year's employment with Sherritt Gordon Mines were obtained and identification information as well as details of work history were collected and placed on computer. Cancer cases were identified by matching the study records with the computer listings of the Alberta Cancer Registry. Cancer deaths were verified utilizing record-linkage with death registrations of the Alberta Vital Statistics Division. The files of the Alberta Health Care Insurance Commission were used to ascertain the vital status of past employees of Sherritt Gordon Mines Limited. Among the 993 employees in the nickel refining and maintenance groups at Sherritt Gordon Mines, 30 cases of cancer were identified occurring at 13 diagnostic sites. No neoplasms of the nasal cavities or paranasal sinuses were found in the study population. Two cases of lung cancer were detected among maintenance workers. A single case of renal-cell cancer was diagnosed in the nickel-exposure category as well as in the maintenance group. None of the observed-to-expected cancer incidence ratios at the various diagnostic sites were statistically significant at the p less than 0.05 level.

58. CANCER MORTALITY ASSOCIATED WITH THE HIGH-TEMPERATURE OXIDATION OF NICKEL SUBSULFIDE

Roberts RS. Julian JA. Muir DC. Shannon HS
Programme in Occupational Health, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.
IARC Sci Publ: 53:23-35 1984

An historical prospective mortality study of INCO's Ontario work-force has been conducted. A cohort of approximately 54,000 men, employed in all aspects of the extraction and refining of copper and nickel from the Sudbury ore deposit, have been followed for mortality between 1950 and 1976. A total of 5,283 deaths were identified by computerized record-linkage to the Canadian Mortality Data Base of death certificates. The analysis focuses on mortality from cancer of the nasal sinuses, larynx, lung, and kidney. Little evidence was found for increased mortality from laryngeal or kidney

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cancer, but lung and nasal cancer deaths were clearly elevated in men exposed to the two Sudbury area sinter plants and at Port Colborne in the leaching, calcining, and sintering department. The standardized mortality ratio (SMR) for lung cancer increases linearly with increasing duration of exposure and there is no evidence of a threshold. The nasal cancer mortality rate also rises linearly with duration of exposure. While lung cancer has a greater excess in the Sudbury sinter plant than at Port Colborne, the reverse is true for mortality from nasal cancer, which is ten times more frequent at Port Colborne than at Sudbury.

59. MORTALITY AMONG WORKERS IN A NICKEL REFINERY AND ALLOY MANUFACTURING PLANT IN WEST VIRGINIA

Enterline PE

Dept. Biostatistics, Graduate Sch of Public Health, Univ. Pittsburgh, Pittsburgh, PA. 15261

JNCI. 68(6):925-933 1982

Workers from a nickel refinery at Huntington, W. Va., which received a nickel matte from smelters in Ontario, Canada, during 1922-47 were studied for excesses in sinonasal and lung cancers. Other workers who were in a nickel alloy production plant operated in conjunction with the refinery but who did not work in the refinery were also studied. Evidence is presented on the existence of a nasal cancer hazard and possibly a lung cancer hazard among workers employed in the nickel refinery. Two of th ese workers developed a sinonasal cancer. Evidence of a respiratory cancer hazard in other parts of the plant before or after 1947 is weak, and the observed results could be due to chance variations from the mortality experience of the standard reference populations. Among nonrefinery workers hired while the nickel refinery was in operation, 2 employees had a probable sinonasal cancer. The first employee worked in a high-temperature conversion process where nickel carbonate was decomposed to nickel oxide, and the second employee is believed to have done maintenance work in the plant where this process was used. For both cohorts combined there were slight overall excesses in lung, stomach, and prostate cancers with some evidence of a dose-response relationship for these cancers. (Author abstract) (11 Refs)

60. MORTALITY IN ONTARIO NICKEL WORKERS (MEETING ABSTRACT)

Roberts RS

Department of Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

J Occup Med. 24(4):332 1982

This presentation will describe the design and major findings of a large mortality study of Ontario nickel workers. The research design is a conventional historical prospective approach with mortality over a 27 year period ascertained through linkage with the Canadian National Mortality Data Base of death certificates. An analysis of cause-specific standardized mortality ratios will be presented by major occupational subgroups within the work force (miners, millers, furnance workers, etc) and concentrate on various respiratory cancers and kidney cancer. Finally, the presentation will investigate the occurrence of unusual patterns of cancer mortality in other sites in what might be described as a 'controlled scientific fishing expedition.' (no Refs)

61. NICKEL AND CANCER ASSOCIATIONS FROM A MULTICANCER OCCUPATION EXPOSURE CASE-REFERENT STUDY: PRELIMINARY FINDINGS

Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R

Departement de medecine du travail et d'hygiene du milieu, Universite de Montreal, Canada.

IARC Sci Publ: 53:105-15 1984

Since 1979 our group has been engaged in a case-referent study of 12 tumour types (oesophagus, stomach, colon, rectum, liver, pancreas, lung, melanoma of skin, prostate, bladder, kidney, lymphoid tissue) and occupational exposure. The study covers the entire Montreal population of males aged 35-70; cases are ascertained in all major hospitals. The interview concerns various sociodemographic variables and a detailed job history. Each job history is evaluated by a team of chemists who infer for each job what the possible physical and chemical exposures were. The list of exposures thus inferred is added to the subject's data file. Each site and each exposure noted in any patient's history are statistically evaluated for possible association. Until June 1982, 1 343 cancer cases and 144 general population subjects had been thus interviewed. For the present purpose, all 1 487 files were reviewed to assign exposure to nickel, and nickel exposure was attributed to 79 subjects. Mantel-Haenszel analyses were carried out comparing each site with a referent group consisting of all other interviewees (other sites and healthy controls). Only the nickel-lung association turned out to be remarkable, with an odds ratio of 3.1, 95% confidence limits 1.9-5.0, and some indication of dose-response effect. The risk was particularly high among stainless-steel welders, though other nickel-exposed workers were also at risk. These findings probably reflect a real risk; however, we cannot be certain that nickel is responsible. Exposure to chromium compounds was so highly correlated with nickel that the observed nickel association may simply have reflected a confounding effect of chromium. Confounding with other occupational exposures is also possible.

5.

Occupational Exposure to Other Specific Chemicals

62. EPIDEMIOLOGIC STUDY OF WORKERS EXPOSED TO ACRYLONITRILE: AN UPDATE

O'Berg MT, Chen JL, Burke CA, Walrath J, Pell S

E.I. du Pont de Nemours and Co., Inc., Employee Relations Department, Wilmington, DE 19898.

J Occup Med: 27(11):835-40 1985

A previous report presented the cancer morbidity and mortality experience through 1976 of a cohort of 1,345 male employees with potential for exposure to acrylonitrile at a fibers-producing plant. This study has now been updated through 1983 for cancer incidence and through 1981 for mortality. Overall, 43 cancer cases have occurred, with 37.1 expected based on company rates. A previously reported excess number of cases of lung cancer remains, but is not as marked (10 observed, 7.2 expected). Prostate cancer cases were significantly in excess, with six cases observed and 1.8 expected. Mortality analyses revealed 36 cancer deaths, with 31.6 expected. Of these, 14 were from lung cancer, with 11.6 expected based on company rates. Only one death from prostate cancer occurred, with 1.0 expected. To our knowledge, prostate cancer excesses have not been reported in any other acrylonitrile studies, and hence their significance is currently difficult to assess.

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63. MORTALITY EXPERIENCE OF EMPLOYEES WITH OCCUPATIONAL EXPOSURE TO DBCP

Hearn S. Gitt MG. Kolesar RC. Cook RR
U.S. Area Medical. Dow Chemical. Midland. Michigan
Arch Environ Health. 39(1):49-55 1984

Concern about the carcinogenic potential of 1,2-dibromo-3-chloropropane (DBCP) has arisen recently, focusing on six organ sites: stomach, liver, kidney, lung, testes, and skin. To examine the mortality experience of persons potentially exposed, a cohort of 550 employees involved in production and formulation from 1957 to 1976 was defined. A total of 35 deaths was observed through 1979 (39.2 expected). No statistically significant excess was observed for any cause of death. No cancer deaths were noted for five of the hypothesized sites. For the lung cancer category, five deaths were observed (2.7 expected, P greater than.135), two of which occurred in a subgroup directly exposed for at least 1 yr (0.5 expected, P greater than.077). Aside from arsenicals exposure, potential confounding resulting from smoking or multiple chemical exposures could not be evaluated.

64. CONGENITAL MALFORMATIONS, MORTALITY AND STYRENE EXPOSURE

Harkonen H. Tola S. Korkala ML. Hernberg S
Institute of Occupational Health. Helsinki. Finland
Ann Acad Med Singapore. 13(2 Suppl):303-7 1984

The prevalence of congenital malformations among children born to styrene-exposed male and female workers, as well as the mortality of the exposed workers, was studied. A cohort of 2,209 workers (1,698 men, 511 women) was selected from the personnel files of 160 workplaces using styrene in the manufacture of reinforced plastic products. The earliest exposure histories began in 1960, but the majority of workers had been exposed after 1967. The data on children born to the exposed workers were linked with those of the Register of Congenital Malformations. The number of malformations of children born to the workers was, both before and during the styrene exposure, below the expected values. In the cohort there were 37 observed deaths (expected 74.0), six of which were due to cancer (expected 13.0). The cancer sites were the stomach (2 cases), bronchus (1), breast (1), ovary (1), and kidney (1 case) There were no cases of lymphatic or haematopoietic cancer. Most of the cancers appeared after short exposure times and soon after the commencement of exposure.

65. MORTALITY AMONG WORKERS FROM A PLASTICS PRODUCING PLANT: A MATCHED CASE-CONTROL STUDY NESTED IN A RETROSPECTIVE COHORT STUDY

Marsh GM
Dept. Biostatistics. Graduate Sch. Public Health. Univ. Pittsburgh. Pittsburgh. PA. 15261
J Occup Med. 25(3):219-230 1983

Earlier proportional mortality studies of workers in a plastics producing plant in Massachusetts indicated excess mortality from certain digestive and genitourinary cancers. To more definitively examine mortality among these workers a retrospective cohort study was conducted for 2,490 male wage earners who worked at least 1 yr during 1949-1966. Vital status was determined as of December 31, 1976, for 99.7% of the cohort and death certificates were obtained for 98.0% of 603 observed deaths. Comparison with the local county white males revealed a slight excess in digestive system cancer (standard mortality ratio [SMR] = 101.8) and a statistically significant excess (p less than 0.05) in genitourinary cancer (SMR = 153.6). A relationship was suggested between cancer of the rectum, liver, and pancreas and both the duration and interval from onset of exposure. A secondary matched case-control study was conducted to determine if particular jobs or work areas were related to the excesses found in the primary study. This analysis did not support the hypothesis that digestive or genitourinary cancer was related to a general plant exposure or date of hire. Possible associations warranting continued surveillance were found between rectal cancer and cellulose nitrate production and between prostatic cancer and polystyrene processing. Digestive and genitourinary cancers other than rectal and prostate were not related to employment in any of 21 occupation exposure categories examined. (Author abstract) (35 Refs)

66. MORTALITY AMONG PULP AND PAPER WORKERS

Milham S Jr. Demers RY
Epidemiology Section. Washington State Department of Social and Health Services. Olympia.
J Occup Med. 26(11):844-6 1984

Mortality among 2,113 U.S. and Canadian members of the Pulp, Sulfite, and Paper Workers' Union, 1935 through 1964, was studied using a proportionate mortality analysis. Mortality due to gastric cancer was found to be elevated in all jurisdictions, but only in mills using sulfate or sulfite pulping. An excess of mortality due to kidney cancer was limited to mills in Oregon and Washington. Excesses of deaths due to leukemia, Hodgkin's disease, and lymphosarcoma were observed only in mills in Oregon, Washington, and Wisconsin and the province of Quebec. Based on small numbers, excesses of deaths due to cancers of rectum, pancreas, kidney, and lymphosarcoma were seen primarily among sulfite process workers, while Hodgkin's disease deaths occurred primarily in sulfate (kraft) process workers. These findings suggest that cancer mortality in pulp and paper workers may be related both to pulping process and to tree species processed.

67. MORTALITY PATTERNS AMONG EMBALMERS

Walrath J. Fraumeni JF Jr
Environmental Epidemiology Branch. National Cancer Institute. Bethesda. MD
Int J Cancer. 31(4):407-11 1983

In view of recent findings of nasal cancer in rats exposed to formaldehyde vapors, we investigated the proportionate mortality experience of embalmers licensed to practice in New York State. Mortality was significantly elevated for cancers of the skin and colon and for arteriosclerotic heart disease, whereas significant deficits were seen in mortality from respiratory diseases and accidents. Respiratory cancer mortality was not excessive and no deaths were attributed to nasal cancer. Mortality was significantly elevated for cancers of the skin, kidney, and brain among those licensed only as embalmers, whereas mortality patterns were unremarkable among those licensed also as funeral directors (and presumably less exposed to formaldehyde) These preliminary results indicate the need for occupational cohort studies to clarify the carcinogenic potential of formaldehyde.

68. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY

Lindstedt G. Sollenberg J
Chemistry Dept., Natl. Board Occupational Safety and Health. S-171 84 Solna. Sweden
Scand J Work Environ Health. 8(1):1-19 1982

Aspects of occupational exposure to polycyclic aromatic hydrocarbons (PAH) are reviewed, with emphasis on benzo[a]pyrene (BAP). PAH are widely distributed in the environment and are associated with industrial processes including coking and combustion of carbonaceous materials.

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Concentrations of PAH in the air in industrial areas are generally 2-3 orders of magnitude less than concentrations in the workplace. The primary sources of PAH are coal tar and pitch. Exposure occurs through the lungs and skin. Samples of PAH are collected on glass fiber or silver film filters and extracted with solvents. Total PAH may be determined or individual compounds may be analyzed by chromatographic methods. Review of studies conducted in various countries indicates that very high exposure to BAP [greater than 10 ug/cubic meter (m3)] occurs in gas and coke works, aluminum works, manufacture of carbon electrodes, handling of molten tar or pitch, chimney sweeping, and use of asphalt mixed with tar. High exposure occurs in blast furnaces and steel works. Findings of epidemiologic studies are contradictory, but some studies indicate an increased risk of lung, bladder, and skin cancers with exposure to PAH. The current threshold limit for exposure to BAP is 0.2 mg/m3. (88 Refs)

69. BLADDER TUMOURS AMONG RODENT OPERATIVES HANDLING ANTU

Davies JM. Thomas HF. Manson D
Div. Epidemiology, Chemistry, Inst. Cancer Res., Sutton, Surrey SM2 5PX, England
Br Med J; 285(6346):927-931 1982

The rodenticide ANTU (alpha-naphthylthiourea) was used in the United Kingdom mainly in the late 1940s and early 1950s. The product then contained up to 0.2% of beta-naphthylamine as an impurity, and it was finally withdrawn in 1967 as a suspected carcinogen. Fourteen cases of urothelial tumors among rodent operatives exposed to ANTU are reported; in one district 4 out of 27 staff were affected, and in another area 2 out of 10. These cases strongly suggest that the early ANTU manufactured in the United Kingdom posed a cancer hazard to users. ANTU is still made or used in various countries, though the current product may be relatively pure and no longer contaminated by beta-naphthylamine. Recent laboratory evidence shows that even pure ANTU is mutagenic in the Ames test, and the safety of this rodenticide may need review. (Author abstract) (24 Refs)

70. CENSUS-BASED MORTALITY STUDY OF FERTILISER MANUFACTURERS

Fraser P. Chilvers C. Goldblatt P
Dept. Medical Statistics and Epidemiology, London Sch. Hygiene and Tropical Medicine, London WC1E 7HT, England
Br J Ind Med; 39(4):323-329 1982

This study was designed to investigate whether exposure to nitrate-containing dust during fertilizer manufacture was associated with an excess of deaths from cancer in general or specifically from cancers of the digestive tract, liver, lung, and bladder. It was based on data extracted from census schedules by the Office of Population Censuses and Surveys, occupational characteristics recorded by fertilizer workers at the 1961 and 1972 censuses of England and Wales being related to subsequent mortality ascertained through the National Health Service Central Register. The 1961 cohort, followed up until 1978, showed a 'healthy worker effect' and no evidence of excess mortality from cancer at any site. The 1971 cohort also showed below av mortality during 1971-7 for all causes of death and for circulatory diseases, but there were more deaths from cancer than expected, due mainly to an excess of cancers of the lung and digestive tract. The excess of cancer was more pronounced, but not statistically significant, when compared with other employed men. Though the numbers of comparison were small, there was weak evidence of an association between cancer mortality and frequency of exposure to nitrate-containing dust in this cohort. It is difficult to reconcile the excess cancer mortality in the 1971 cohort with the more favorable level in the earlier cohort, since industrial hygiene has improved and the cohorts showed a similar distribution by region and social class. To examine further these conflicting results the 1971 cohort will be followed for a longer period and re-examined when more deaths have accrued. (Author abstract) (33 Refs)

71. BLADDER CANCER IN THE ALUMINIUM INDUSTRY

Theriault G. Tremblay C. Cordier S. Gingras S
School of Occupational Health, McGill University, Montreal, Quebec, Canada.
Lancet; 1(8383):947-50 1984

The incidence of bladder cancer is unusually high in aluminium smelter workers. An epidemiological study showed that workers in Soderberg potrooms are at highest risk for bladder cancer, the adjusted overall relative risk being 2.39 (1.34-4.28). Exposure to polycyclic aromatic hydrocarbons, of which benzo(a)pyrene (BaP) served as an indicator, seems to be the causative factor. The relative risk was evaluated at 12.38 for workers with 20 or more equivalent years of BaP exposure. Cigarette smoking contributed significantly to the appearance of bladder cancer in the population studied. There is a synergistic effect when cigarette smoking and BaP exposure are combined; the numbers in our population are too small to determine whether this interaction effect is multiplicative or additive. It is concluded that bladder cancer is associated with aluminium smelting (primarily with the Soderberg process).

72. MORTALITY STUDIES OF ALUMINUM REDUCTION PLANT WORKERS: POTROOM AND CARBON DEPARTMENT

Rockette HE. Arena VC
Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, PA.
J Occup Med; 25(7):549-57 1983

The purpose of this study was to investigate mortality patterns of aluminum reduction plant workers. A cohort was formed of 21,829 workers with five or more years employment in 14 reduction plants. Progress of the study was reported quarterly to a Tripartite Committee consisting of representatives from labor, management and government. Although the results of other studies relative to an excess of lung cancer in aluminum workers were not confirmed, there were indications of a higher than expected mortality in pancreatic cancer, lymphohematopoietic cancers, genitourinary cancer, nonmalignant respiratory disease and benign and unspecified neoplasms.

73. MORTALITY EXPERIENCE AMONG CHROMEPLATING WORKERS. INITIAL FINDINGS

Franchini I. Magnani F. Mutti A
Institute of Semeiotica Medica, University of Parma, Italy.
Scand J Work Environ Health; 9(3):247-52 1983

A retrospective cohort study was conducted in nine chromeplating plants to examine the mortality of workers employed for at least one year during the period January 1951-December 1981. The study group totaled 178 individuals, 116 of whom were from 'hard' and 62 from 'bright' chromeplating plants. Vital status ascertainment was 97% complete. The total number of deaths was fairly close to the expected figure (15 observed, 15.2 expected), whereas deaths from tumors exceeded the expected number (8 observed, 4.2 expected). Individuals were distinguished into two subcohorts depending on the exposure intensity, which was much higher in hard than in bright chromeplating. Most deaths from cancer occurred among hard chromium platers, the excess against the expected rate being statistically significant (7 observed,

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2.7 expected, p = 0.02). All deaths from lung cancer occurred in this subcohort (3 observed, 0.7 expected, p = 0.03). The increased mortality from cancer among chromium platers seems to be related to exposure intensity and strongly suggests the need for further studies on larger cohorts to confirm the carcinogenicity of chromic acid in man.

74. MORTALITY OF LEAD SMELTER WORKERS

Seleton SG, Landrigan PJ, Stern FB, Jones JH
Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH
Am J Epidemiol; 122(4):673-83 1985

To examine patterns of death in lead smelter workers, a retrospective analysis of mortality was conducted in a cohort of 1,987 males employed between 1940 and 1965 at a primary lead smelter in Idaho. Overall mortality was similar to that of the United States white male population (standardized mortality ratio (SMR) = 98). Excess mortality, however, was found from chronic renal disease (SMR = 192; confidence interval (CI) = 88-364), and the risk of death from renal disease increased with increasing duration of employment, such that after 20 years employment, the standardized mortality ratio reached 392 (CI = 107-1.004). Excess mortality was also noted for nonmalignant respiratory disease (SMR = 187, CI = 128-264). Eight of 32 deaths in this category were caused by silicosis; at least five workers who died of silicosis had been miners for a part of their lives. An additional 11 deaths resulted from tuberculosis (SMR = 139; CI = 69-249); in six of these cases, silicosis was a contributory cause of death. Cancer mortality was not increased overall (SMR = 95; CI = 78-114). An increase, however, was noted for deaths from kidney cancer (six cases; SMR = 204; CI = 75-444). Finally, excess mortality was noted for injuries (SMR = 138; CI = 104-179); 13 (23%) of the 56 deaths in this category were caused by mining injuries. The data from this study are consistent with previous reports of increased mortality from chronic renal disease in persons exposed occupationally to lead.

75. MORTALITY AMONG EMPLOYEES OF LEAD BATTERY PLANTS AND LEAD-PRODUCING PLANTS, 1947-1980

Cooper WC, Wong O, Kheifets L
Environmental Health Associates, Inc, Oakland, California
Scand J Work Environ Health; 11(5):331-45 1985

Two cohorts of male lead workers, 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least one year during the period 1 January 1946 through 31 December 1970, were observed for mortality during the 34 years from 1 January 1947 through 31 December 1980. Vital status as of the closing date was determined for 94.7% of the former group and 91.6% of the latter. There were 1,718 deaths in the first cohort and 621 in the second. Mortality from all causes combined was significantly greater than expected in each cohort, the standardized mortality ratio (SMR) being 107 and 113, respectively. Among the battery plant workers the greater than expected mortality rate resulted in large part from a significant number of excess deaths from malignant neoplasms (SMR 113), other hypertensive disease (mainly renal) (SMR 320), chronic nephritis (SMR 222), and a group of ill-defined conditions (SMR 355). Among the lead production workers the pattern was similar, with a significant number of excess deaths from other hypertensive disease (SMR 475), hypertensive heart disease (SMR 203), chronic nephritis (SMR 265), and ill-defined conditions (SMR 214). There was also a significant excess of deaths from external causes (SMR 143). The SMR for total malignancies was 113, but this value was not significantly elevated at the 5% level. In neither cohort were deaths from cerebrovascular disease in significant excess, the SMR being 93 and 132, respectively. A proportionate mortality analysis showed that the excess deaths from cerebrovascular disease and from hypertensive heart disease among smelter workers were in part due to the high proportion of nonwhites in the smelter populations. The stomach, liver, and lungs were the sites responsible for most excess cancer deaths in both cohorts, but the elevated SMR values were statistically significant only for gastric and lung cancers in battery plant workers. There were no excess deaths from malignancies of the kidney, brain, or lymphopoietic system in either cohort. It is impossible to relate the observed mortality to levels of lead exposure; because of meager quantitative information prior to 1960. It is known that past exposures had been very high. Ethnicity, diet, alcohol, and cigarette smoking could not be ruled out as possible confounding etiologic factors for the cancer deaths.

76. MORTALITY PATTERNS AMONG STAINLESS-STEEL WORKERS

Cornell RG
Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor.
IARC Sci Publ; 53:65-71 1984

Mortality patterns were studied for former workers at plants of seven companies in the United States engaged in the production of stainless and low nickel alloy steels. All deaths were included for at least a five-year period up to the end of 1977 for each plant. Age at death, whether or not the potential for exposure to nickel existed, sex, race and cause of death were recorded. Data on 4 882 deaths, including complete data on 4 487 deaths of white males, were obtained. An age-standardized proportional mortality analysis of the 4 487 deaths of white males showed that there was a slightly lower proportion of deaths from cancer, and specifically from cancer of the lung or kidney, than would be expected from the age-specific proportional mortality patterns observed in the United States as a whole. This holds regardless of whether or not there was the potential for exposure to nickel. No exposure effect was substantiated apart from variation among plants. Furthermore, no nasal cancers were observed either for white males or others, which strongly indicates that the problem previously observed among nickel refinery workers with respect to nasal cancer does not exist among workers engaged in the production and processing of stainless and low nickel alloy steels.

C.
Urinary Tract or Prostate Cancer Due to Occupational Exposure to Unidentified Industrial Chemicals

1.
Occupational Exposure to Unidentified Chemicals in Rubber Industry

77. MORTALITY AMONG RUBBER WORKERS: X. RECLAIM WORKERS

Delzell E, Monson RR
Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115.
Am J Ind Med; 7(4):307-13 1985

This study evaluated the mortality experience of 1,352 white and 438 nonwhite men who worked in the rubber-reclaiming division of a large rubber manufacturing company. In comparisons of mortality of white reclaim workers with that of

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nonreclaim workers rate ratios were 2.7 for esophageal cancer (six observed deaths among reclaim workers), 2.1 for bladder cancer (seven observed deaths), and 4.5 for multiple myeloma (six observed deaths). The excess of bladder cancer among white reclaim workers may be associated with their employment in other high-risk areas of the plant, whereas no such explanation was found for the excesses of esophageal cancer and multiple myeloma. Overall, the lung cancer mortality rate of white reclaim workers was similar to the rate of US white males and other white rubber workers. There was a 50% excess of lung cancer deaths among nonwhite reclaim workers compared with other nonwhite rubber workers. However, this observation is based on small numbers, and no firm conclusions can be reached about the risk of lung cancer associated with reclaim operations in this group of rubber workers.

78. MORTALITY AMONG RUBBER WORKERS: VIII. INDUSTRIAL PRODUCTS WORKERS

Delzell E. Monson RR
Department of Epidemiology, Harvard School of Public Health, Boston.
Am J Ind Med; 6(4):273-9 1984

This report compares the mortality experience of 6,533 men employed in the industrial products division of a rubber manufacturing company with that of U.S. males and of other rubber workers. For most causes of death the mortality rates of industrial products workers were lower than those of U.S. males and similar to those of other rubber workers. Relative to other rubber workers, men in the industrial products division had a 50% excess of deaths from lymphoma, a 90% excess of deaths from multiple myeloma, and a 20% excess of deaths from bladder cancer during the study period. The excesses of lymphoma and multiple myeloma were strongest during recent follow-up in 1970-78 (observed/expected deaths: 10/4.3 for lymphoma; 10/4.4 for multiple myeloma), whereas bladder cancer mortality was not excessive during this calendar period.

79. MORTALITY AMONG RUBBER WORKERS: VII. AEROSPACE WORKERS

Delzell E. Monson RR
Department of Epidemiology, Harvard School of Public Health, Boston.
Am J Ind Med; 6(4):265-71 1984

This study evaluated cause-specific mortality among 3,161 men who were employed in the aerospace division of a rubber manufacturing company. Compared to other production workers at the plant, aerospace workers in deicer and fuel cell manufacturing jobs experienced a 60% excess of deaths from lung cancer. Deicer and fuel cell workers who were under 65 years of age had lung cancer rates that were approximately twice those of other rubber workers of comparable age. Aerospace division employees also had elevated rates of bladder cancer, leukemia, lymphoma, and multiple myeloma. However, detailed analyses suggested that, with the exception of lung cancer, these cancer excesses were not likely to be attributable to employment in the aerospace division.

80. TRANSITIONAL CELL CARCINOMA OF THE UPPER RENAL TRACT IN RUBBER WORKERS

Chapple CR. Neuman J. O'Brien JM. Considine J
Department of Urological Surgery, East Birmingham Hospital, UK.
Postgrad Med J; 61(719):837-8 1985

We report two patients where transitional cell carcinoma of the upper urinary tract developed after occupational exposure to known carcinogens, in the rubber industry. Although carcinoma of the bladder is well recognized in this context, to our knowledge, this association has not been reported previously.

81. CANCER MORTALITY AND SOLVENT EXPOSURES IN THE RUBBER INDUSTRY

Wilosky TC. Checkoway H. Marshall EG. Tyroler HA
Occupational Health Studies Group, School of Public Health, University of North Carolina, Chapel Hill.
Am Ind Hyg Assoc J; 45(12):809-11 1984

Some evidence suggests that solvent exposures to rubber industry workers may be associated with excess cancer mortality, but most studies of rubber workers lack information about specific chemical exposures. In one large rubber and tire-manufacturing plant, however, historical documents allowed a classification of jobs based on potential exposures to all solvents that were authorized for use in the plant. A case-control analysis of a 6678 member cohort compared the solvent exposure histories of a 20% age-stratified random sample of the cohort with those of cohort members who died during 1964-1973 from stomach cancer, respiratory system cancer, prostate cancer, lymphosarcoma, or lymphatic leukemia. Of these cancers, only lymphosarcoma and lymphatic leukemia showed significant positive associations with any of the potential solvent exposures. Lymphatic leukemia was especially strongly related to carbon tetrachloride (OR = 15.5, p less than.0001) and carbon disulfide (OR = 8.9, p = .0003). Lymphosarcoma showed similar, but weaker, associations with these two solvents. Benzene, a suspected carcinogen, was not significantly associated with any of the cancers.

82. RETROSPECTIVE COHORT STUDY OF TWO PLANTS IN THE SWEDISH RUBBER INDUSTRY

Holmberg B. Westerholm P. Maasing R. Kestrup L. Gumaelius K. Holmlund L. Englund A
Unit of Occupational Toxicology, National Board of Occupational Safety and Health, Solna, Sweden.
Scand J Work Environ Health; 9 Suppl 2:59-68 1983

A cohort of 13,114 workers employed during 1930-1975 in two Swedish plants producing tires and industrial rubber goods was investigated with regard to cancer mortality and cancer incidence. Separate analyses were performed on the following subgroups of the cohort: mixers/weighers, other production workers, and white-collar employees. For all causes of death no increase of risk was observed in the population as a whole. Mixers/weighers showed however an increased overall standardized mortality ratio. The pattern of causes of death was not changed in the total cohort. An increased risk to die from liver cancer (risk ratio 4.12) and pancreatic cancer (risk ratio 2.70) was, however, observed for the category other production workers. An increased risk of death from tumors of the respiratory organs was also observed for the categories other production workers (risk ratio 1.89) and white-collar employees (risk ratio 2.63). For tumors in the urinary bladder (risk ratio 2.50) and for ischemic heart diseases (risk ratio 1.27) the death risk was elevated for the category other production workers. The cancer morbidity pattern showed an increase in malignant melanomas (risk ratio 2.50) for the category other production workers and for lung cancer (risk ratio 2.09), as well as for tumors in the nervous system (risk ratio 3.18) for white-collar employees.

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83. RUBBER WORK AND CANCER - PAST, PRESENT AND PERSPECTIVES

Nutt A
Dunlop Limited, Dunlop Technology Division, Birmingham, United Kingdom
Scand J Work Environ Health: 9 Suppl 2:49-57 1983

In the early years, the study of health in the rubber industry was hampered by lack of information in three fields. Epidemiology was just beginning, industrial hygiene had hardly begun, and little or no work had been done on the ways in which rubber chemicals affect the human body. The difficulties this created can clearly be seen in the problems of bladder cancer discovered in the industry in 1949. Since that time epidemiologic studies have become very detailed, more results are available on concentrations of material in factory atmospheres, and the effects of different chemicals on the body are being better understood. This review considers the historical problems of beta-naphthylamine exposure, summarizes the epidemiologic results on the industry to date, and considers the potential problems posed by polycyclic aromatic hydrocarbons and nitrosamines. (29 Refs)

84. CANCER MORTALITY IN THE BRITISH RUBBER INDUSTRY

Parkes HG, Veys CA, Waterhouse JA, Peters A
Dept. Social Medicine, British Rubber Manufacturers' Assoc., Birmingham, England
Br J Ind Med: 39(3):209-220 1982

Although it is over 30 years since an excess of bladder cancer was first identified in British rubber workers, the fear has persisted that this hazard could still be affecting men working in the industry today. Furthermore, suspicions have also arisen that other and hitherto unsuspected excesses of cancer might be occurring. For these reasons 38,815 men, who first started work in the industry between 1 January 1946 and 31 December 1960, have been followed up to 31 December 1975 to ascertain the number of deaths attributable to malignant disease and to compare these with the expected number calculated from the published mortality rates applicable to the male population of England and Wales and Scotland. The findings confirm the absence of any excess mortality from bladder cancer among men entering the industry after 1 January 1951 (the presumed bladder carcinogens were withdrawn from production processes in July 1949), but they confirm also a statistically significant excess of both lung and stomach cancer mortality. A small excess of esophageal cancer was also observed in both the tire and general rubber goods manufacturing sectors. American reports of an excess of leukemia among rubber workers receive only limited support from the present study, where a small numerical excess of deaths from leukemia is not statistically significant. A special feature of the study is the adoption of an analytical method that permits taking into account the long latent period of induction of occupational cancer. (Author abstract) (56 Refs)

85. CANCER INCIDENCE AMONG FINNISH RUBBER WORKERS

Kilpikari I, Pukkala E, Lehtonen M, Hakama M
(c/o Hakama) Finnish Cancer Registry, Liisankatu 21 B, SF-00170 Helsinki 17, Finland
Int Arch Occup Environ Health: 51(1):65-71 1982

Risk of cancer among male and female workers was evaluated in the footwear, tire processing, and tire and tube fabrication departments of a rubber plant, where cancer risk was reported to have increased consistently. A total of 1,331 workers, who had been employed for 3 mo or more, were followed for cancer through the files of the Finnish Cancer Registry from 1953-1976 for a total of 11,709 person yr, more than half of which occurred under age 35 yr. Chemical exposure was mostly of a mixed type originating from chemical dust and solvent vapor. The 21 cases of observed cancer did not differ significantly from the 18.9 (relative risk [RR] 1.1) expected. RR showed no consistent trend with age; RR was 1.3 among males, and 0.8 among females. There was no significant increase in the number of tumors at specific anatomic sites, although the RR at selected sites were 1.4 for digestive and 1.5 for respiratory organs. Two bladder tumors were diagnosed; the expected number was 0.3. The RR for the study population as a whole was 1.1 while it was 2.0 for those with more than 10 or 20 yr of follow up. (19 Refs)

86. SEARCH FOR CARCINOGENIC AGENTS IN THE SHANGHAI RUBBER INDUSTRY (MEETING ABSTRACT)

Wang HW, You XJ, Qu YH, Wang WF, Wang D, Long YM, Ni JA, Dzeng RW
Shanghai Inst. of Cell Biology, Academia Sinica
Environ Sci Res: 31:825 1984

Preliminary studies on crude cancer incidences (1961-1970) among workers of 89 factories in Shanghai revealed excessive cancer risks to workers in certain rubber type factories. Three 2-yr in situ animal exposures staged in the First Workshop of Rubber Tire Factory A showed that compounding and banbury mills for mastication and mixing were the origins of carcinogenic pollutants. These results prompted reconstruction of the workshop and suspension of the use of antioxidant D in Shanghai. All 8 chronic experiments carried out in different institutes by feeding, injection and inhalation of technical and pure phenyl-2-naphthylamine (PBNA), especially to the lungs, of rats and mice, indicated carcinogenicity. Repeated sc injections of both technical and chemically pure PBNA dissolved in DMSO resulted in 45% of male ICR mice developing malignant tumors within 10 mo. Results of the determinatio n of atmospheric concentration of PBNA at different sites in two rubber tire factories suggested a relationship between PBNA in air and lung cancers of the workers. The alpha-isomer of PBNA, N-phenyl-l-naphthylamine (PANA) is the main constituent of antioxidant A, also a widely used rubber additive, the carcinogenicity of which had never been suspected before. Its biological effect was compared with PBNA in chronic injection experiments with ICR and TA1 mouse strains. Both tests showed a similar carcinogenic potency. PANA had a tendency to induce hemangiosarcomas. Previous unilateral nephrectomy enhanced induction of renal hemangiosarcomas by both chemicals. The approximately similar carcinogenic potency of PANA (technical and pure) and PBNA suggests routes of metabolic activation other than dephenylation of PANA and PBNA in mice.

87. CALCULATING CANCER LATENCY USING DATA FROM A NESTED CASE-CONTROL STUDY OF PROSTATIC CANCER (MEETING ABSTRACT)

Goldsmith Dr
Dept. of Community and Family Medicine, Univ. of California, San Diego, CA
Time Related Factors in Cancer Epidemiology, May 15-17, 1985, Bethesda, Maryland, 1985.

Assessing latency for neoplastic diseases is crucial for determining the causal effects of a mix of complex carcinogenic exposures. Initial assessment of cancer risks in a US tire and rubber plant revealed a significant SMR of 140 for prostatic cancer. Using an industry-based, case-control death certificate study of prostatic malignancies, we found matched odds ratios of about 3 (p less than 0.025) for Batch Preparation, the work area with the greatest exposure to dust, solvents,

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and heavy metal oxides. We used the matched case-control series to make annual estimates of the odds ratio by determining the proportion of cases and controls employed for greater than 1 mo in Batch Preparation during the yr under study. To reduce variability in the resulting curve, a method was developed that measured the 'etiologic fraction,' which at its highest point represents an estimate of the latency period. The modal point was 29 yr before death with the greatest risk occurring from employment in Batch Preparation in 1946. The latency method allows risk assessment for time and yr of greatest exposure difference, thus suggesting appropriate prevention strategies. Applications of this method for other types of studies and exposures were discussed. Comparison with other methods of latency estimation, including the serially additive dose model, was also presented.

2.

Occupational Exposure to Unidentified Chemicals in Chemical Industry

88. A CASE-CONTROL STUDY OF RENAL CANCER MORTALITY AT A TEXAS CHEMICAL PLANT

Bond GG. Shellenberger RJ. Flores GH. Cook RR. Fishbeck WA
Dou Chemical U.S.A.. Midland. Michigan.
Am J Ind Med: 7(2):123-39 1985

An in-plant case-control study of 26 renal cancer deaths was conducted to determine whether an occup ational exposure may be related to an apparent increase in mortality from this disease observed among a sample of employees at a multiple process chemical production facility. None was found that explained the excess. Elevated odds ratios were identified for employment in the cell maintenance area of chlorine production and with those presumptive exposures considered to occur in this job, asbestos and caustic, but not chlorine. While an association between renal cancer and asbestos has been previously reported, an association with caustic, per se, is not consistent with prior observations made by others. Diminished risk estimates were observed for employment in magnesium production and for exposures in this process to sulfur dioxide and heat. Both the increased and decreased risks, while statistically significant, are based on small numbers of exposed subjects and may be spurious owing to the problem of multiple comparisons.

89. MORTALITY AMONG A SAMPLE OF CHEMICAL COMPANY EMPLOYEES

Bond GG. Reere GR. Ott MG. Waxweiler RJ
Dou Chemical U.S.A.. Midland. Michigan.
Am J Ind Med: 7(2):109-21 1985

A general mortality survey was done on a 5% random-start systematic sample (N = 1,666) of present and former white male employees of a Texas chemical plant. The purpose was to determine whether there were any unusual patterns of cause-specific mortality that would require further research with case-control studies. Mortality risks were examined by duration of employment and year of hire as surrogates for more specific exposure data. Among all employees in the sample, there was significant excess mortality due to All Cancer, Ill-Defined Conditions, and All External Causes of Death, and a significant deficit from All Circulatory Diseases. The excess mortality from All Cancer was primarily attributable to excess cancers of the kidney, lung, and pancreas. The excesses for lung and kidney cancer were statistically significant. Those employed for 1 year or more experienced significantly lower mortality from All Causes than those employed for less than 1 year.

90. URINARY CYTOLOGY IN WORKMEN ENGAGED IN THE PETROCHEMICAL INDUSTRY WITH REFERENCE TO NON-INDUSTRIAL RISK FACTORS

Adolphs HD. Hildenbrand G. Schwabe HW. Vahlensieck EW
Department of Urology. University. Bonn. Federal Republic of Germany.
Urol Res: 13(2):61-5 1985

Urine cytology was evaluated in 8,406 male workers of 8 petrochemical factories in western and northern Germany during the routine medical check-up performed by the department of industrial medicine of the respective factory. All relevant data referring to possible private and occupational risk factors were registered and evaluated. Four percent (n = 358) of the 8,406 workers examined exhibited Pap 3/4 cytology. Urological examination did not reveal any bladder tumor in those workers with either a single Pap 4 or a repeated Pap 3 finding on cytology. Our study showed that deterioration of cell differentiation correlated significantly with age and cigarette smoking. Furthermore, a risk group (males above 40 years of age exposed to occupational chemicals, smokers, and coffee drinkers) differed from a non-risk group. Age and cigarette smoking seemed to be the determinant factors. No correlation could be adduced between any kind of industrial exposure and urine cytology.

91. OCCUPATIONAL HEALTH EXPERIENCE WITH ORGANIC ADDITIVES

Thiess AM. Wellenreuther G
Occupational Medicine and Health Protection. BASF Aktiengesellschaft. Ludwigshafen. Federal Republic of Germany.
Regul Toxicol Pharmacol: 4(4):340-9 1984

For many decades, interest in occupational medicine has been focused on the wide variety of organic additives, which includes a large number of substances, for example, dyestuffs, pigments, and auxiliaries for the textile, leather, and paper industries. The reason is that, if the recommended precautions are not observed, there is a risk of exposure to most of these substances during both production and use. Moreover, over the years, some additives have caused concern and aroused suspicion regarding adverse effects on health. In order to deal with health problems in this field, it is important to be aware of how, what, and where occupational diseases or accidents arise. Much knowledge has been gained about these, and it would be an impossible task to give a systematic survey of the data that have accumulated, especially since it is necessary to take account of the problem of exposure to more than one substance. Thus an attempt is made to report on occupational health experience in general, and to demonstrate how an industrial hygienist may approach the many and various problems. Some epidemiological studies on organic additives (auramine, anthraquinone dyestuffs, organic dyes, etc.) are discussed.

92. CANCER MORBIDITY AND EXPOSURE TO TRICHLOROETHYLENE (MEETING ABSTRACT)

Axelson O. Andersson K. Selden A. Hogstedt C
Dept. of Occupational Medicine. S-581 85 Linkoping. Sweden
International Conference on Organic Solvent Toxicity. October 15-7. 1984. Stockholm. Sweden. p. 126. 1984.

Trichloroethylene (TRI) is widely used in industry. Its biotransformation involves an epoxide and TRI has shown mutagenicity in some test systems. Liver and lung tumors have appeared in experiments using mice but epidemiology has been inconclusive. An earlier presented Swedish cohort of workers, surveyed by trichloroacetic acid (TCA) analyses in the urine, has now been updated and extended to encompass 1424 men. Exposure took place through 1975; and the cohort is still relatively young and with 65% exposed after 1969.

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More than 90% of the workers had average TCA levels less than 100 mg/l. Expected cancers were calculated from the age specific rates provided by the Swedish cancer register, wh ich also permitted the identification of individuals with cancer through 1979. The overall results as obtained for various exposure and latency requirements are presented in a table. A corresponding mortality analysis was also made and, somewhat surprisingly, different results were obtained, ie, there was a deficit of cancer deaths (22 cancers vs 36.9 expected). The excess morbidity derived from a few sites, ie, 3 urinary bladder cancers vs 0.83 expected, 4 cancers of the prostate vs 2.35 expected and 2 lymphomas vs 0.27 expected, with an exposure requirement of 2 years or more and 10 years of latency. It remains unclear if TRI is causally associated with the excess of cancers or if other phenomena or concomitant exposures could play a role, eg, stabilizers such as diisopropylamine and possibly epichlorohydrin and epoxybutane. (1 Ref)

3.

Occupational Exposure to Unidentified Chemicals in Petroleum-Related Occupations

93. EPIDEMIOLOGIC EVIDENCE FOR AN ASSOCIATION BETWEEN GASOLINE AND KIDNEY CANCER

Enterline PE, Viren J
Center for Environmental Epidemiology, Graduate School of Public Health, University of Pittsburgh, PA 15261.
Environ Health Perspect; 62:303-12 1985

A recent animal experiment suggests that gasoline exposure may be a cause of human kidney cancer. This is a literature review to see whether there is any epidemiologic support for these animal findings. Trends and geographic patterns in gasoline consumption and kidney cancer mortality are moderately supportive of a relationship, although this cannot be considered important evidence for a causal relationship. Most other ecological correlations are not supportive of a relationship. Eleven oil refinery populations and one population of petroleum products distribution workers have been studied. These studies taken as a group do not appear to support the notion of a relationship between gasoline exposure and kidney cancer. However, most were not designed or analyzed with this hypothesis in mind. An examination of these data which attempts to consider the ages of the populations studied provides some evidence of a small kidney cancer excess among older workers or among workers exposed for long periods. Because of the importance of gasoline and the potential for exposure by the public further study of exposed populations is needed.

94. PETROLEUM-RELATED EMPLOYMENT AND RENAL CELL CANCER

McLaughlin JK, Blot WJ, Mehl ES, Stewart PA, Venable FS, Fraumeni JF Jr
Biostatistics Branch, National Cancer Institute, Bethesda, Md 20205.
J Occup Med; 27(9):672-4 1985

The risk of renal cell cancer among those in occupations with potential for petroleum exposure was evaluated in a large population-based case-control study. Overall there was little difference between the cases and control groups in the proportion of persons with petroleum-related employment (odds ratio = 1.0). Among gasoline station attendants, a slight upward trend in risk was observed with increasing duration of employment. The significance of this association is not clear, but further research is needed in light of recent animal findings linking gasoline exposure to renal cancer.

95. EPIDEMIOLOGIC STUDIES OF THE ROLE OF GASOLINE (HYDROCARBON) EXPOSURE IN KIDNEY CANCER RISK

Wen CP, Tsai SP, Moffitt KB, Bondy M, Gibson RL
Gulf Oil Corp., P.O. Box 2100, Houston, TX 77252
Adv Mod Environ Toxicol; 7:245-57 1984

The role of gasoline exposure in the development of kidney cancer among oil company employees was studied in the following seven different data sets: (1) a study of kidney cancer mortality in Jefferson and Orange counties, Texas; (2) a cohort study of Gulf Oil Corporation's Port Arthur (Texas) refinery; (3) a mortality surveillance study of Gulf's total employees and annuitants; (4) a cancer incidence study of Gulf's refinery and petrochemical plants; (5) a historical mortality study of Gulf's employees by proportionate mortality ratio analysis; (6) a case-control study of the refinery cohort; and (7) a comparison of the gasoline exposure of refinery workers with that of workers at marketing terminals and gasoline stations. Despite increases in kidney cancer mortality in the United States in recent years, the data sets examined containing workers with potential gasoline exposure did not show an increase over and above what would have been expected. This was true both for workers in the refinery (inside the fence) and for residents in the communities (outside the fence). Statistically nonsignificant increases in kidney cancer risk were observed in the case-control study in relation to smoking and alcohol usage. None of the kidney cancer data examined showed increases at the 5% level; this is particularly noteworthy for the case-control study which, using two sets of controls, failed to show any significant increase from potential exposure to gasoline in any of sixteen job/department groups. (9 Refs)

96. THE EPIDEMIOLOGY OF RENAL CARCINOMA IN HUMANS WITH A NOTE ON THE EFFECT OF EXPOSURE TO GASOLINE

Higginson J, Muir C, Buffler PA
Unit. Associated for Res. and Education in Pathology, Inc., 9650 Rockville Pike, Bethesda, MD 20814
Adv Mod Environ Toxicol; 7:203-26 1984

The epidemiology of cancer of the renal parenchyma in humans is reviewed, inferences are drawn as to the etiology, and the question of the potential role of gasoline in human cancers is considered. The incidence of renal carcinoma is highest in Scandinavia and lowest in Asia, and is higher in males than in females. Moderate urban-rural and intra-country differences are observed in some countries. There have been no marked increases in incidence observed in recent years. The major etiologic factor identified is cigarette smoking, which probably explains much of the demonstrated differences over time and place. Gasoline exposure does not appear to be a plausible factor in explaining the higher renal carcinoma frequencies seen in Iceland and Scandinavia as compared with southern Europe. There is no evidence to support the view that significant changes in the incidence of renal cancer in the general population of the United States and elsewhere have occurred as a result of the three- to five-fold increase in the use of gasoline and gasoline products since 1950. It is more likely that where such changes in incidence have been observed, they can be explained, in large part, by modifications in diagnostic practices and smoking. No satisfactory hypotheses are available, however, to explain the wide variations in incidence among countries. None of the studies of refineries and related occupations have shown a significant and consistent association between renal cancer and employment in different segments of the oil industry. Variations in cohorts, in duration of employment, and in levels of exposure limit direct comparisons. (59 Refs)

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97. KIDNEY CANCER EPIDEMIOLOGY IN PETROLEUM-RELATED STUDIES

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Mobil Oil Corp., 150 E. 42nd St., New York, NY 10017
Adv Mod Environ Toxicol: 7:259-71 1984

Eight occupational analytical and two ecological studies of petroleum industry countries were each reviewed with respect to excess of kidney cancer, using the schema developed by Hill for assessing causal inference. Positive answers to questions of strength of association, dose-response effect, lack of temporal ambiguity, consistency of findings, biological plausibility and coherence, and specificity of association contribute to the conclusion of a causal relationship. The analytical studies included standardized mortality ratios, standardized incidence ratios, and proportionate mortality ratio analyses. The ecologic studies consisted of comparisons of rates between geographic areas; information was available on the population residing in those areas but not on individuals within the population. It was generally impossible, therefore, to control for confounding and bias, and the results of the ecological studies were not useful in assessing causal relationships. Overall, kidney cancer did not appear to be in excess in petroleum refining populations. However, as hydrocarbon exposure was not homogeneous in these populations, the data should be reexamined, or new studies started, to examine hydrocarbon dose response (and lifestyle) and to establish firmly the lack of association. Only one of the studies dealing with job subcohorts moved in this direction. An excess of kidney cancer observed among drivers relative to the overall cohort was a concern, because the deficit in lung cancer argues against a high percentage of smokers. While the data that were reviewed did not suggest any kidney cancer excess in petroleum refinery populations and were inconclusive for distribution workers, the gaps in information on exposure, dose, lifestyle confounding, and latency analyses argue strongly for additional study. (23 Refs)

98. TEXACO MORTALITY STUDY. I. MORTALITY AMONG REFINERY, PETROCHEMICAL, AND RESEARCH WORKERS

Divine BJ, Barron V, Kaplan SD
Texaco Inc., Houston, TX.
J Occup Med: 27(6):445-7 1985

The Texaco mortality study is a retrospective follow-up study of all persons who were employed for at least five years in a refining, petrochemical, or research facility and who worked at some time during the period 1947 through 1977. Of the 19,077 white men in the cohort, 14,609 were alive, 4,024 were known to be dead, and the vital status of the remaining 444 was unknown as of Dec. 31, 1977. The standardized mortality ratio (SMR) of 75 for all causes was significantly low, on the basis of 5,332 expected deaths. Statistically significant deficits also were seen for all major causes of death and for cancer of many sites, including lung, stomach, bladder, and colon. The SMR was greater than 100 for six causes of death: pancreas cancer, brain cancer, leukemia, Hodgkin's disease, other lymphatic cancer, and benign neoplasms. However, none of these increases was statistically significant, and all SMRs except that for benign neoplasms (SMR = 148) were under 119.

99. LONG-TERM MORTALITY STUDY OF OIL REFINERY WORKERS. IV. EXPOSURE TO THE LUBRICATING-DEWAXING PROCESS

Wen CP, Tsai SP, Weiss NS, Gibson RL, Wong O, McClellan WA
Gulf Oil Corporation, Houston, TX.
JNCI: 74(1):11-8 1985

A retrospective cohort mortality study of 1,008 male oil refinery workers who ever worked on the lubricating-dewaxing process of the lube oil department and who have been followed for a period of 43 years is presented. These workers were exposed to a number of solvents, primarily methyl ethyl ketone [(MEK) CAS: 78-93-3] and toluene (CAS: 108-88-3), but at levels far below the current Occupational Safety and Health Administration's standard. The standardized mortality ratio (SMR) for all causes (0.70) and the SMR for cancer (0.86) are much lower than unity when they are compared to the mortality experience of the U.S. population. Also observed in this study were 8 prostate cancer deaths (4.4 expected) with an SMR of 1.82, which was not statistically significant (P = .16). Seven of these 8 prostate cancer deaths occurred among nonwhite males, who showed an SMR of 2.47 (P = 0.53). However, only 1 prostate cancer death was seen among workers specifically assigned to the MEK units. The remaining deaths occurred among maintenance workers who had lube oil department-wide assignments. This cancer risk increased with increasing duration of employment in the lube oil department. A latency of 20 years or more was also observed for these prostate cancer deaths. In this study the processing of lubricating oils was found to be at least as important as the MEK solvents, and department-wide maintenance workers were as much at risk as the MEK unit workers. In view of this finding and findings obtained by others, it seems prudent to continue to study lubricating-dewaxing process workers, including the medical monitoring of all such workers for prostate cancer.

100. LONG-TERM MORTALITY STUDY OF OIL REFINERY WORKERS. I. MORTALITY OF HOURLY AND SALARIED WORKERS

Wen CP, Tsai SP, McClellan WA, Gibson RL
Medical and Health Resources Division, Gulf Oil Corporation, Houston, TX.
Am J Epidemiol: 118(4):526-42 1983

This longitudinal study examined the mortality and cancer experience of workers at the Gulf Oil refinery located in Port Arthur, Texas. The cohort was studied over a period of 41 years, from 1937 to 1978, and consisted of 16,880 employees, with an accumulation of 406,198 person-years; 4361 deaths were observed. Emphasis of this study was placed on the experience of the hourly and salaried male workers employed one day or more and those with a minimum of one year employment. The standardized mortality ratio analysis revealed generally favorable mortality experience of the refinery workers, including that of overall cancer. Statistically significant deficits in mortality were found for several cancer sites including bladder, liver, and esophageal cancer. Many of the increased cancer risks suggested in the literature were not confirmed in this study. Although bone cancer was found to be increased significantly, review of those death certificates raises questions as to the accuracy of the recording and coding of this cancer. Sample size of this study is capable of providing sufficient statistical power for the detection of a twofold increase in mortality risk for many cancers, if such risk exists.

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101. EPIDEMIOLOGIC STUDY OF REFINERY AND CHEMICAL PLANT WORKERS

Hanis N.M. Holmes T.M. Shallenberger L.G. Jones K.E.
Exxon Corporation, P.O. Box 235, E. Millstone, NJ 08873
J Occup Med; 24(3):203-212 1982

A dynamic retrospective cohort study was performed to examine the mortality experience of workers at Exxon's Baton Rouge, La, refinery and chemical plant. Included were 8,666 regular employees who worked at least 1 mo during the period January 1, 1970 through Dec 31, 1977, and retirees who were alive as of Jan 1, 1970. Mortality from all causes of death was lower than expected when compared with that of the U S population of similar age, sex, and race. Analyses of mortality by specific site of cancer revealed elevated standardized mortality ratios (SMRs) for cancer of the kidney, testis, brain/central nervous system, pancreas, and lymphopoietic sites; none of these elevations was statistically significant. Because of the higher than av mortality from cancer of the pancreas in some Louisiana parishes and the observation that one additional death from cancer of the pancreas in this study would have resulted in a statistically significant SMR at the 95% confidence level, some emphasis was placed on this finding. No evidence was found to link cancer of the pancreas to a specific occupational group. An examination of mortality by occupational class revealed some elevated SMRs for further study. (Author abstract) (24 Refs)

102. A PROPORTIONATE MORTALITY STUDY OF AN OIL, CHEMICAL AND ATOMIC WORKERS LOCAL IN TEXAS CITY, TEXAS

Reeve G.R. Thomas T.L. Kelly V.F. Waxweiler R.J. Itaya S
Biometry Section, Industrywide Studies Branch, Natl. Inst. for Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, OH. 45226
Ann NY Acad Sci; 381:54-61 1982

A proportionate mortality ratio (PMR) study was conducted of deceased members of the Oil, Chemical and Atomic Workers Union in Texas City, Texas in order to determine whether unusual patterns of cancer mortality exist in petrochemical plants and refineries. A total of 264 white union members who died after 1947 were included in the study, and two refineries (A and B) were analyzed in depth. In Refinery A, the PMR for nonmotor vehicle accidents was elevated (12 deaths observed vs 7.36 expected) and that for all cancer was only slightly elevated (1.18). However, excess deaths from skin cancer (PMR = 7.88), brain and CNS neoplasms (4 observed vs 1.57 expected), kidney cancer (2 observed vs 0.84 expected), and liver cancer (3 observed vs 0.64 expected) were observed. In Refinery B, excess deaths from lung cancer (6 observed vs 3.86 expected; not statistically significant) and hematopoietic and lymphatic cancer (4 observed vs 1.22 expected) were observed. Thus, deaths due to skin, brain, liver, and kidney cancer at Refinery A and deaths due to hematopoietic and lymphatic cancer at Refinery B were proportionately in excess. The relative excess of melanoma deaths observed at Refinery A appears to represent an occupationally related health problem. The relative excess of other cancer deaths at these refineries warrant further study. (18 Refs)

103. EXPOSURE OF OIL REFINERY WORKERS TO THE LUBRICATING-DEWAXING PROCESS [LETTER]

Mantel N
JNCI; 75(1):180-1 1985

Keywords (MeSH): Carcinogens/adverse effects; Human; *Industry; Male; Occupational Diseases/*chemically induced/mortality; Prostatic Neoplasms/mortality; Time Factors.

4.

Occupational Exposure to Automobile Exhaust

104. MOTOR EXHAUST-RELATED OCCUPATIONS AND BLADDER CANCER

Silverman DT. Hoover RN. Mason TJ. Swanson GM
Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, Maryland 20892.
Cancer Res; 46(4 Pt 2):2113-6 1986

The relationship between employment in occupations with potential exposure to motor exhaust and bladder cancer risk was examined based on interviews conducted with 1909 white male bladder cancer patients and 3569 population controls during the National Bladder Cancer Study, a population-based, case-control study conducted in ten areas of the United States. Our findings indicated that males usually employed as truck drivers or deliverymen have a statistically significant, 50% increase in risk of bladder cancer. Overall, a statistically significant trend in risk with increasing duration of truck driving was observed. This trend was particularly consistent for drivers first employed at least 30 years prior to diagnosis. Of these, truck drivers employed 25 years or more experienced a 120% increase in risk. Elevations in risk were also suggested for taxicab and bus drivers. These findings, coupled with experimental evidence of the mutagenicity and possible carcinogenicity of motor exhaust emission particulates, suggest a role for motor exhaust exposure in human bladder carcinogenesis.

105. TRUCK DRIVING AND BLADDER CANCER MORTALITY IN RURAL NEW ENGLAND

Hoar SK. Hoover R
Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD 20205-8200.
JNCI; 74(4):771-4 1985

The relationship between truck driving and bladder cancer mortality was investigated in a case-control study in New Hampshire and Vermont. In-person interviews were conducted with the next-of-kin of 325 bladder cancer cases and 673 controls who died during 1975-79. There were 35 cases and 53 controls who had ever been employed as truck drivers [odds ratio (OR)=1.5, 95% confidence interval (CI)=0.9, 2.6]. There was a statistically significant, but inconsistent, positive association between number of years of truck driving and the OR's, rising to 2.3 (1.2,4.1) for 5 years or more of truck driving. Risk was greatest in men who began driving in the 1930's and 1940's (OR=2.6, 95% CI=1.3,5.1) and among residents of two of the most urbanized counties (OR=3.0, 95% CI=1.2,7.4). The association of bladder cancer with truck driving was unaffected by control for possible confounding factors, such as cigarette smoking and coffee drinking. It was not possible to determine whether the risks associated with truck driving were specifically due to diesel fumes. Truck drivers reporting diesel exposures had an OR=1.8 (95% CI=0.5,7.0), but those without diesel exposure still had an OR=1.5 (95% CI=0.8,2.7). Twenty-six cases and 39 controls reported exposure to diesel emissions in any occupation (OR=1.5, 95% CI=0.8,2.8), and a significant duration-response relationship was seen, rising to threefold for those employed in such jobs for 30-39 years.

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106. BLADDER CANCER RISK AMONG AUTO AND TRUCK MECHANICS AND CHEMICALLY RELATED OCCUPATIONS

Smith EM. Miller ER. Woolson RF. Brown CK
Department of Preventive Medicine and Environmental Health. College of Medicine. University of Iowa. Iowa City 52242.
Am J Public Health: 75(8):881-3 1985

Male participants in the NCI National Bladder Cancer study were evaluated for risks in auto and truck mechanic and in chemically related exposure occupations compared with those who had never worked in these areas. In nonsmokers the adjusted rate ratios (RR) for mechanics equalled 1.33, (95% CI 0.77 , 2.31). The adjusted RR in the nonsmoker chemically related group was 1.53 (95% CI 1.13, 2.07). Duration of exposure as a mechanic was not clearly associated with bladder cancer risk regardless of smoking status.

107. A CASE-CONTROL STUDY OF DIESEL EXHAUST EXPOSURE AND BLADDER CANCER

Wynder EL. Dieck GS. Hall NE. Lahti H
Mahoney Institute for Health Maintenance. American Health Foundation. New York. New York 10017.
Environ Res: 37(2):475-89 1985

The relationship between bladder cancer and employment in occupations involving exposure to diesel exhaust was examined using data from a hospital-based case-control study of men aged 20 to 80 years in 18 hospitals in six U.S. cities, from January 1981 to May 1983. In this analysis, 194 cases and 582 controls were compared according to occupation, smoking history, alcohol and coffee consumption, and various demographic variables. No difference was found in the proportion of bladder cancer cases employed in occupations with exposure to diesel exhaust compared to controls. This relationship did not change after taking smoking habits into account. Bladder cancer cases were significantly more likely to be current smokers of cigarettes than were controls.

5.

Occupational Exposure to Unidentified Chemicals in Shoe and Leather Industry

108. BLADDER CANCER AND OCCUPATIONAL EXPOSURE TO LEATHER

Marrett LD. Heritage P. Meigs JW
Department of Epidemiology and Public Health. Yale University. New Haven. CT.
Br J Ind Med: 43(2):96-100 1986

A large case-control study of bladder cancer (2982 cases; 5782 controls) included information about occupational exposure to leather. Occupational histories of exposed white study subjects were reviewed and 150 were determined to have had 'true' on the job exposure to leather. The odds ratio estimate (OR) of bladder cancer associated with such exposure in white subjects (n = 8063) was 1.4 (95% confidence limits = 1.0, 1.9) after adjustment for sex, age, and cigarette smoking. The risk was highest in those first employed in a leather job before 1945, although no dose-response relation with duration of leather employment was found. Subjects employed in 'dusty' leather jobs had a slightly higher risk than those with other types of leather jobs. Our results are consistent with reports of an increased risk of bladder cancer associated with exposure to leather. Although the agents responsible have not been identified, our findings of an increased risk associated with exposure in the earlier years of this century and in dusty jobs suggest that leather dusts may be important.

109. CANCER MORTALITY AMONG SHOE AND LEATHER WORKERS IN MASSACHUSETTS

Garabrant DH. Wegman DH
Occupational Health Program. Harvard School of Public Health. Boston. MA.
Am J Ind Med: 5(4):303-14 1984

A proportional mortality analysis of death certificates of 2,798 shoe and leather workers demonstrated a statistically significant excess of bladder cancer among female shoe workers (PMR = 2.51, 95% confidence interval 1.23 to 5.12). A case-referent analysis of 289 leather workers, on whom detailed occupational information was available, demonstrated an association of lung cancer with work in leather-tanning jobs (odds ratio = 4.2, 95% confidence interval 1.09 to 16.2).

110. PROPORTIONATE MORTALITY AMONG US SHOEWORKERS, 1966-1977

Decoufle P. Walrath J
School of Health Related Professions. University of Arizona. Tucson.
Am J Ind Med: 4(4):523-32 1983

Proportionate mortality for various causes was examined among 3,754 decedents (2,144 men, 1,610 women) who had worked in shoe manufacturing plants represented by either of two labor unions in the US. None of the shoeworker deaths were attributed to nasal cancer, whereas 2.2 were expected on the basis of general population data. Mortality from leukemia and cancer of the urinary bladder was not unusual in either sex or either union. However, deaths from cancers of the liver and gallbladder combined were significantly increased among male and female members of one union. Three deaths from mesothelioma were seen among members of this same union. Rectal cancer mortality was higher than expected among men and women in both unions. The findings are at variance with previous reports of high risks of certain cancer sites among shoeworkers. However, results for liver and gallbladder cancer and mesothelioma suggest the possibility that other previously unsuspected hazards may have been present in certain areas of the US shoe industry.

111. KIDNEY CANCER AMONG LEATHER WORKERS [LETTER]

Malker HR. Malker BK. McLaughlin JK. Blot WJ
Lancet: 1(8367):56 1984

Keywords (MeSH): Female; Human; Kidney Neoplasms/*occurrence; Male; Occupational Diseases/*occurrence; Sweden; *Tanning.

112. KIDNEY CANCER AMONG LEATHER WORKERS [LETTER]

Acheson ED. Pippard EC
Lancet: 1(8376):563 1984

Keywords (MeSH): Human; Kidney Neoplasms/*occurrence; Male; Occupational Diseases/*occurrence; *Tanning.

113. KIDNEY CANCER AMONG LEATHER WORKERS [LETTER]

Carturight RA. Boyko RW
Lancet: 1(8381):850-1 1984

Keywords (MeSH): England; Human; Kidney Neoplasms/*mortality; Male; Occupational Diseases/*mortality; *Tanning.

6.

Occupational Exposure to Unidentified Chemicals in Other Occupations

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114. ASSOCIATIONS BETWEEN SEVERAL SITES OF CANCER AND NINE ORGANIC DUSTS: RESULTS FROM AN HYPOTHESIS-GENERATING CASE-CONTROL STUDY IN MONTREAL, 1979-1983

Siemiatycki J. Richardson L. Gerin M. Goldberg M. Dewar R. Desy M. Campbell S. Wacholder S

Centre de Recherche en Epidemiologie et Medecine Preventive. Institut Armand-Frappier. Laval-des-Rapides. Quebec. Canada.

Am J Epidemiol: 123(2):235-49 1986

A multi-cancer site, multi-factor case-control study was undertaken to generate hypotheses about pos sible occupational carcinogens. Probing interviews were carried out with over 2,000 subjects. All incident cases of 19 sites of cancer in males aged 35-70 and resident in Montreal were eligible. The interview was designed to obtain detailed lifetime job histories, and information on potential confounders. Each job history was reviewed by a team of chemists who translated it into a history of occupational exposures. These occupational exposures were then analyzed as potential risk factors in relation to the sites of cancer included. For each site of cancer analyzed as a case series, controls were selected from among the other cancer sites in the study. This report concerns the associations between sites of cancer for which there were over 100 cases processed (stomach; colorectal, also analyzed by subsites; lung; prostate; bladder; kidney; non-Hodgkin's lymphoma) and nine organic dusts (wood; paper; grain; flour; fabrics; cotton; wool; synthetics; fur). All site-exposure combinations were investigated. The ones that provided the most interesting leads were lung-wood dust (odds ratio (OR) = 1.5), stomach-wood dust (OR = 1.5), colorectal-synthetic fiber (OR = 1.5), bladder-synthetic fiber (OR = 1.8), non-Hodgkin's lymphoma-cotton dust (OR = 1.9), colon-grain dust (OR = 2.6), prostate-grain dust (OR = 2.2), and prostate-paper dust (OR = 2.0). Only the associations with wood dust, synthetic fibers and cotton dust showed some evidence of 'dose-response' with duration of exposure. Because it is such a common exposure and appears to increase lung and stomach cancer risks, wood dust may be responsible for a great deal of occupational cancer.

115. DEATH CERTIFICATE CASE-CONTROL STUDY OF CANCERS OF THE PROSTATE AND COLON AND EMPLOYMENT IN THE TEXTILE INDUSTRY

Hoar SK. Blair A

Environmental Epidemiology Branch. National Cancer Institute. Bethesda. MD.

Arch Environ Health: 39(4):280-3 1984

A case-control study was conducted to investigate possible relationships between employment in the textile industry and cancers of the prostate and colon. Death certificate information on occupation and industry was obtained for 1037 male prostatic cancer cases, 820 male and female colon cases, and matched controls who died during 1970-1978 in South Carolina. Black males were the only race-sex group to show an excess risk of prostate or colon cancer among employees of the textile industry. Nonstatistically significant excesses of prostate cancer were seen in dyeing and finishing businesses and broad woven fabric mills. Overall, there was no strong evidence indicating a relationship between the textile industry and either prostate or colon cancer. It is unlikely that limitations of the data masked real risks since previously reported associations with nontextile industries were confirmed.

116. INTEGRATION OF LABORATORY AND EPIDEMIOLOGIC STUDIES TO EVALUATE GENOTOXIC EXPOSURE IN TOOL AND DIE W ORKERS

Garry VF. Jacobs DR. Kreiger RA. Nelson RL. Loeppky R. Harkins ME

Department of Laboratory Medicine. University of Minnesota 55455.

Prog Clin Biol Res: 207:183-93 1986

In summary, the data presented here provides perspective on the analysis of cancer in a relatively small population of tool and die workers. Each part of the effort establishes evidence for or against the presence of a workplace carcinogenic effect. Overall, the weight of evidence leads to the hypothesis that cutting fluids are a likely candidate for observed increases in urinary system cancer and perhaps other sites. Because cutting fluids and a wide variety of metals are used together, the interaction of these entities need be considered in the overall process of carcinogenesis in the workplace.

117. A PROPORTIONAL MORTALITY RATIO STUDY OF WORKERS IN FARM IMPLEMENT AND DIESEL ENGINE MANUFACTURING

Mallin K

Univ. of Illinois at Chicago. Health Sciences Center. Chicago. IL

Diss Abstr Int [BI: 46(1):131 1985

A Proportional Mortality Ratio (PMR) analysis and Proportional Cancer Mortality Ratio (PCMR) analysis were done of workers at an International Harvester plant in Illinois which has produced crawler tractors and diesel engines since 1946. The industrial processes used as the plant include machining, solvent cleaning, welding, brazing, heat treating, assembly and engine testing, with exposures to cutting oils, solvents, and metal fumes and dust. A total of 461 deaths occurred between 1970 and 1982, with 351 deaths to whites, and 110 to blacks. PMRs and PCMRs were calculated using the Illinois and local county distribution of deaths as the standard, and PMRs were also calculated using the US standard population. In most cases, Illinois PMRs and PCMRs were similar to the county and national results. Among whites, non-malignant deficits were found for respiratory and digestive deaths, but the PMRs were not statistically significant. No excess of cancer or other causes of death were found. No site specific cancers were significantly in excess for white males in either the PMR and PCMR analysis, for all such deaths, and for the group with 20 or more years of employment. However, statistical power was low for most sites except lung. A moderate and non-significant excess of deaths from prostate and stomach cancer and from malignant melanoma were also found for whites. Among blacks, a significant excess of all neoplasms was found, but the distribution of other non-malignant causes of death was near expectation. A significant excess of cancer of the pancreas, malignancies of the lymphatic and hematopoietic system, and non-Hodgkin's lymphomas was found in the PMR analysis, and for non-Hodgkin's lymphoma in the PCMR analysis. All of the deaths for these cancer sites occurred to workers with 20 or more years of employment. A moderate but insignificant excess of cancer of the prosta te and multiple myeloma was also found for blacks. When the white and black deaths for these two sites were analyzed together, the PMRs were significantly above expectation. The combined PCMRs were also excessive, but were not significant. (Author abstract)

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118. CUTTING OILS AND BLADDER CANCER [LETTER]

Vineis P, Di Prima S

Scand J Work Environ Health; 9(5):449-50 1983

Keywords (MeSH): Bladder Neoplasms/*chemically induced; Human; Male; *Metallurgy; Occupational Diseases/*chemically induced; Oils/*adverse effects.

119. A COHORT MORTALITY STUDY OF PAINTERS AND ALLIED TRADESMEN

Matanoski GM, Stockwell HG, Diamond EL, Haring-Sweeney M, Joffe RD, Mele LM, Johnson ML

Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland 21205.

Scand J Work Environ Health; 12(1):16-21 1986

A cohort study was conducted of the membership of a large international union of painters and allied tradesmen. The union membership consisted of both painters and associated trades such as glaziers and tile and carpet layers. The study examined the mortality experience of 57 175 current and former union members in four states (California, Missouri, New York, and Texas) in the United States (US) from 1975 through 1979. No excess mortality was observed for the total union membership when compared to that of all US white males. When the study population was subdivided by the trade affiliation, members of locals comprised primarily of painters exhibited a significant elevation in mortality from all malignant neoplasms, lung cancer, and stomach cancer, compared to all US white males. To reduce the impact of potential nonoccupational differences between the study population and all US white males, the data were also analyzed using the entire cohort as the standardization population. Significant elevations continued to be observed for all malignant neoplasms and lung cancer among the membership of painting locals compared to other locals. In addition there was a statistically significant difference in mortality from leukemia and cancer of the bladder observed between the groups.

120. OCCUPATIONAL EXPOSURES AMONG FATHERS OF CHILDREN WITH WILMS' TUMOR

Wilkins JR, Sinks TH Jr

Department of Preventive Medicine, Ohio State University, Columbus.

J Occup Med; 26(6):427-35 1984

An occupation-and-exposure linkage system was utilized to perform an epidemiologic case-control study of paternal occupation and Wilms' tumor in offspring. The first part of the study was designed to test the hypothesis that paternal lead (Pb) exposure is a risk factor for Wilms' tumor in offspring. The second part of the study was an exploratory analysis that sought to generate possible etiologic hypotheses about other paternal exposures in the workplace in relation to Wilms' tumor. Calculation of odds ratios indicated that there was no statistical difference in the frequency of occupational exposure to Pb, Pb alkyls, and Pb salts for fathers of children with Wilms' tumor and fathers of controls, a finding that contrasts sharply with the results of the one previously reported study in this area. In the exploratory phase of the study, case fathers were found more likely to have been exposed to boron, while control fathers were found more likely to have encountered insecticides, acetylene, o-chlorobenzylidene, oil orange ss, and diethylene glycol; the differences were statistically significant. Troublesome methodologic problems, including exposure misclassification, sample size, and multiple comparisons, are discussed.

121. PATERNAL OCCUPATION AND WILMS' TUMOUR IN OFFSPRING

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Department of Preventive Medicine, Ohio State University, Columbus.

J Epidemiol Community Health; 38(1):7-11 1984

A case-control study was conducted to test the hypothesis that paternal occupation is a risk factor for Wilms' tumour in offspring. Occupations associated with exposure to lead (Pb) and to hydrocarbons were examined by computing odds ratios, all of which were greater than unity but not by a statistically significant margin. When painters were considered separately, children whose fathers had been so employed were six times more likely to develop Wilms' tumour than children whose fathers had other occupations. Like the results for the Pb and hydrocarbon related occupations, the estimated relative risk associated with painters did not reach statistical significance. Although these data require cautious interpretation because of the relatively small number of subjects, the results reported here are not wholly consistent with the results of the one previous study of paternal occupation and Wilms' tumour in offspring.

122. INCREASED RISK FOR MALE BLADDER CANCER AMONG A COHORT OF MALE AND FEMALE HAIRDRESSERS FROM GENEVA

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Medical Inspectorate of Factories, Geneva, Switzerland.

Int J Epidemiol; 14(4):549-54 1985

A cohort of 703 male and 677 female hairdressers born from 1880 onwards, who started to run salons in Geneva between 1900 and 1964 was followed-up to the end of 1982. Cause-specific mortality was analysed from 1942 to 1982 and a significant excess mortality from bladder cancer (observed deaths = 10, expected deaths = 3.9) was found among males. Cancer incidence recorded for the years 1970 to 1980 showed a significant increase among males for all neoplasms (O = 65, E = 51.4), cancer of the buccal cavity and pharynx (O = 6, E = 2.5), cancer of the prostate (O = 12, E = 6.1), and bladder cancer (O = 11, E = 5.3). Among female hairdressers no significant increase in mortality or in cancer incidence was found. Mean age at diagnosis of the 18 deaths and/or incident cases from bladder cancer found among the male hairdressers was 68.6 years (range 51-88) and mean latency period since first expos ure was 52.2 years (range 24-73). Occupational history was obtained for most of the 18 cases and of 54 controls randomly selected from the cohort. Little evidence was found of a causal relationship between exposure to hair dyes and the excess risk for bladder cancer among the male hairdressers. It is a suggestion that this excess might be related to some colouring agent(s) in brilliantines which were widely used in men's hairdressing salons in Geneva until about 1950.

123. USE OF HAIR DYES AND RISK OF BLADDER CANCER

Hartge P, Hoover R, Altman R, Austin DF, Cantor KP, Child MA, Key CR, Mason TJ, Marrett LD, Myers MH, Narayana AS, Silverman DT, Sullivan JW, Swanson GM, Thomas DB, West DW

Div. Cancer Cause and Prevention, Environmental Epidemiology, Branch Field Studies and Statistics Program, 7910 Woodmont Ave., Room 3C06, NCI, Bethesda, MD, 20205

Cancer Res; 42(11):4784-4787 1982

The relation between use of hair dyes and risk of bladder cancer was assessed using data from a case-control study of bladder cancer. Incident cases (2,982) and general population controls (5,782) were interviewed. The overall estimate of

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relative risk of bladder cancer for users of hair dyes was 1.0 (95% confidence interval, 0.9 to 1.2) compared to nonusers. No consistent pattern of association was detected between bladder cancer risk and various indices of timing or intensity of exposure to hair dyes. Various explanations of the lack of association are discussed. (Author abstract) (17 Refs)

124. HAIR DYES: EPIDEMIOLOGICAL EVIDENCE

Kinlen L.
CRC Cancer Epidemiology Unit. Edinburgh. Scotland. UK.
IARC Sci Publ: (65):57-66 1985

Keywords (MeSH): Bladder Neoplasms/chemically induced/occurrence; Breast Neoplasms/chemically induced/occurrence; Female; Hair Dyes/*adverse effects; Hair Preparations/*adverse effects; Human; Male; Neoplasms/*chemically induced/occurrence; Occupational Diseases/chemically induced/occurrence.

125. CANCER RISK AMONG ARTISTIC PAINTERS

Miller BA. Silverman DT. Hoover RN. Blair A
Epidemiology and Biostatistics Program. National Cancer Institute. Bethesda. MD 20892.
Am J Ind Med: 9(3):281-7 1986

An association between bladder cancer and employment as an artistic painter was found in two study populations. A proportionate mortality analysis of death certificates of professional artists indicated a greater than twofold excess for bladder cancer mortality among painters. This association was further investigated in a large case-control interview study of bladder cancer patients where an overall relative risk estimate of 2.5 was found among artistic painters. Excess deaths from leukemia and arteriosclerotic heart disease also occurred in the proportionate mortality study. Information was not available to determine exposure to specific substances that may have been responsible for these observations; however, efforts should be made to limit exposure to art materials known to be hazardous.

126. MORTALITY PATTERNS AMONG PROFESSIONAL ARTISTS: A PRELIMINARY REPORT

Miller BA. Blair A. McCann M
Environmental Epidemiology Branch. National Cancer Institute. Bethesda. MD 20205.
J Environ Pathol Toxicol Oncol: 6(2):303-13 1985

Causes of death among 1598 professional artists were compared with an expected distribution based on the general U.S. population to determine if there were unusual patterns of fatal disease that might be indicative of exposure to hazardous substances in their work environment. Deaths among men and women in the arts were identified from obituaries in Who's Who in American Art published between 1940 and 1969. Among 1253 white male artists, PMRs were significantly elevated for arteriosclerotic heart disease, leukemia and cancers of the bladder, colon, rectum, kidney, and brain. The significant excesses of bladder cancer and leukemia deaths were limited to painters. Proportions of deaths due to colon cancer were significantly elevated among male painters and sculptors. Prostate cancer mortality was slightly higher than expected among painters and significantly elevated among sculptors. Among 345 female artists, painters represented the only specialty category large enough to analyze and excess numbers of deaths due to cancers of the rectum, lung, and breast were noted.

127. MULTIPLE PRIMARY CANCERS, WITH SPECIAL REFERENCE TO OCCUPATIONAL EXPOSURE

Okubo T. Kraus JF. Yamaguchi N. Ishizu S. Sugita M
Department of Epidemiology. University of Occupational and Environmental Health. Fukuoka Prefecture. Japan.
Jpn J Clin Oncol: 15 Suppl 1:243-53 1985

Multiple primary cancer (MPC) relating to occupational exposure was studied. The study consisted of a literature survey, survey of on-going research and our project on the frequency and nature of MPC in an occupational cohort of Japanese dyestuff workers followed from 1962 through 1983. From the review of the literature and on-going research there is little information on MPC and existing findings are mostly incomplete. However, a few occupational agents known to be carcinogenic to more than two organs, i.e. arsenic or radium, have been reported to cause MPC. In our follow-up of occupational bladder cancer cases, increased MPCs compared with a matched control group of nonoccupational cases were observed, but further investigation is necessary for a final conclusion. Finally, epidemiologic problems inherent to the study of MPC, including occupational studies, are discussed.

128. CANCER OF THE BLADDER OCCURRING IN OCCUPATIONAL DYE USERS: REPORT OF TWO CASES

Ando M. Takeda H. Mizuo T. Yokokawa M. Ushiyama T
Department of Urology. Tokyo Rosai Hospital
Hinyokika Kiyo: 30(2):223-8 1984

Two cases of occupational dye users were found to have bladder tumors. Case 1 was a 32-year-old male , who had worked at the Yuzen process for the last 7 years. Multiple papillary tumors were seen on the whole wall of the bladder endoscopically and total cysto-urethrectomy and ileal conduit were performed. The pathological examination of the bladder tumors revealed non-invasive transitional cell carcinoma grade I - II. His post-operative course has been uneventful without any signs of tumor recurrence for 31 months. Case 2 was a 46-year-old male, who had worked at the throwing stained silk for the last 28 years. He suffered from severe hematuria for six months. A big egg-sized nonpapillary tumor on the posterior wall of the bladder was found and bilateral cutaneous-ureterostomy was performed but severe gross hematuria remained. Total cysto-urethrectomy was performed but the patient died of progressive disease 5 months later. The bladder tumor was a grade III invasive transitional cell carcinoma. The fact that process workers in the dye manufacturing industry have a high risk of bladder cancer has been well known and mass screening examination on them has been systematically performed. Though there is a higher relative risk of bladder cancer in occupational dye users, systematic screening examination has not been done. We emphasize the necessity for establishing systematic mass screening examination of occupational dye users for the early diagnosis of bladder cancer.

129. [NINE CASES OF BLADDER CANCER OCCURRING IN OCCUPATIONAL DYE USERS]

Murase T. Takashi M. Aota Y. Shimoji T. Miyake K. Mitsuya H
Department of Urology. Nagoya University School of Medicine.
Hinyokika Kiyo: 31(8):1459-62 1985

Workers in the dye manufacturing industry have a high risk of urinary bladder cancer. There may also be a high relative risk of bladder cancer in occupational dye users. Nine occupational dye users were found to have bladder cancer. The period of engaging with dye work ranged from 5 to 40 years. Seven patients had bladder cancer and the other 2 patients had lesions both in the bladder and in the renal pelvis. His-

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topathology of all cases was transitional cell carcinoma. Three cases were classified into grade 1 and 6 cases into grade 2. One patient died of bladder cancer. The other 8 patients are alive. Four cases recurred after TUR therapy. It is necessary to establish systemic mass screening examination of occupational dye users for the early diagnosis of bladder cancer.

130. CANCER IN THE ELECTRIC POWER INDUSTRY

Tornqvist S. Norell S. Ahlbom A. Knave B
Department of Occupational Neuromedicine. National Board of Occupational Safety and Health. Solna. Sweden.
Br J Ind Med: 43(3):212-3 1986

A cohort study of 3358 power linesmen and 6703 power station operators classified in the 1960 population census in Sweden was undertaken. The cancer incidence between 1961 and 1979 was calculated in relation to all male blue collar workers. The relative risk of cancer (all sites) was 1.1, (1.0-1.2, 90% confidence limit) in the group of power linesmen and 1.0 (0.9-1.0) for power station operators. No consistent excess risk of leukaemia or brain tumour was found in the two occupational groups. In both groups a tendency towards an excess risk of cancer of the urinary organs was found.

131. MORTALITY OF EMPLOYEES OF THE UNITED KINGDOM ATOMIC ENERGY AUTHORITY, 1946-1979

Beral V. Inskip H. Fraser P. Booth M. Coleman D. Rose G
Department of Epidemiology. London School of Hygiene and Tropical Medicine.
Br Med J (Clin Res): 291(6493):440-7 1985

An analysis was conducted of 3373 deaths among 39 546 people employed by the United Kingdom Atomic Energy Authority between 1946 and 1979, the population having been followed up for an average of 16 years. Overall the death rates were below those prevailing in England and Wales but consistent with those expected in a normal workforce. At ages 15-74 years the standardised mortality ratios (SMRs) were 74 for deaths from all causes and 79 for deaths from all cancers. Mortality from only four causes was above the national average - namely, testicular cancer (SMR 153; 10 deaths), leukaemia (SMR 123; 35 deaths), thyroid cancer (SMR 122; three deaths), non-Hodgkin's lymphoma (SMR 107; 20 deaths) - but in none was the increase significant at the 5% level. Half of the authority's employees were recorded as having been monitored for exposure to radiation, their collective recorded exposure being 660 Sv (65 954 rem). Among these prostatic cancer was the only condition with a clearly increased mortality in relation to exposure. Of the 19 men who had a radiation record and died from prostatic cancer at ages 15-74 years, nine had been monitored for several different sources of exposure to radiation. The standardised mortality ratios were 889 (six deaths) in employees monitored for contamination by tritium, 254 (nine deaths) in those monitored for contamination by other radionuclides, and 385 (nine deaths) in those with dosimeter readings totalling more than 50 mSv (5 rem); but the same nine subjects tended to account for each of these significantly raised ratios. Because multiple exposures were common and other relevant information was not available the reason for the increased mortality from prostatic cancer in this population could not be determined and requires further investigation. Excess mortality rates of 2.2 and 12.5 deaths per million person years per 10 mSv (1 rem) were estimated for leukaemia and all cancers, respectively. The confidence limits around these estimates were wide, included zero, and made it unlikely that the International Commission on Radiological Protection's cancer risk coefficients were underestimated by more than 15-fold. Thus despite this being the largest British workforce whose mortality has been reported in relation to low level ionising radiation exposure, even larger populations will need to be followed up over longer periods before narrower ranges of risk estimates can be derived.

132. CANCER INCIDENCE AMONG EMPLOYEES IN ONE MINERAL WOOL PRODUCTION PLANT IN DENMARK

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Danish Cancer Registry. Copenhagen. Denmark.
Scand J Work Environ Health: 10(1):17-24 1984

The initiating hypothesis of the present study was that exposure to respirable fibers from mineral wool in concentrations seen at the place of production is carcinogenic to the respiratory system. In a test of this hypothesis 5,369 employees in the mineral wool production plant in question were followed from first employment at the plant until day of death or until the end of 1977. The factory started producing mineral wool in 1937 and the Danish Cancer Registry started working on a nationwide scale in 1943; therefore there was a maximum 40 years' duration of employment and 35 years' follow-up in the Cancer Registry. The observed numbers of cancer cases were compared with the expected numbers calculated on the basis of the age-, sex-, and time-specific incidence rates for cancer among the Danish population. Within the study period the Registry received notification of 136 cohort members with one cancer and 4 with two primary cancers, ie, a total of 144 cancer cases was observed against the 133.8 expected. Among workers with 20 or more years from first employment in the plant a significant excess of cancer of the lungs, bladder, and skin was found (observed versus expected cases: 9 vs 4.3, 4 vs 1.6 and 5 vs 2.4, respectively). This study thus supports the working hypothesis of an association between lung cancer and mineral wool production when the latency period for this type of cancer is taken into consideration.

133. ANALYSES OF CANCER INCIDENCE IN BLACK GOLD MINERS FROM SOUTHERN AFRICA (1964-79)

Bradshaw E. McGlashan ND. Fitzgerald D. Harington JS
(c/o Harington). Natl. Cancer Assoc. South Africa. P.O. Box 2000. Johannesburg 2000. South Africa
Br J Cancer: 46(5):737-748 1982

As an extension of an earlier study covering the 8-yr period 1964-71 (t1), the incidence of cancer in black gold miners over a second 8-yr period, 1972-79 (t2) has been investigated. The population again totalled 2.9 million man-yr of employment, an av of 363,800 men per yr. Of the 903 cancers found in t2, primary liver cancer accounted for 45.4%, esophageal cancer 19.8%, cancer of the respiratory system 11.2% and bladder cancer 2.7%. Analysis of these four common cancers by country or region of origin of the miners confirms for the most part the patterns of incidence found in the earlier survey and consolidated rates are therefore presented for the full 16-yr period, 1964-79 (t3). The spatial distribution of primary liver cancer within Mozambique and esophageal cancer within Transkei have been investigated for the periods t1, t2 and t3 and temporal changes of rate have been examined by individual yr from 1964 to 1979. The geographical gradient of incidence for cancer of the esophagus in Transkei has become less marked during the second period of the survey and the crude incidence rate for primary liver cancer in gold miners from Mozambique has continued to drop throughout the period of the survey. (Author abstract) (5 Refs)

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134. MORTALITY OF ALUMINUM REDUCTION PLANT WORKERS, 1950 THROUGH 1977

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School of Occupational Health, McGill University, Montreal, Alberta, Canada.
J Occup Med: 27(10):761-70 1985

The mortality experience of 5,406 men (cohort I) employed at one aluminum smelter on Jan. 1, 1950, and 485 men employed at a second plant (cohort II) on Jan. 1, 1951, is reported. For each man, the total number of years of exposure to tars, the number of years since first exposure to tars, and an index of exposure to tars expressed in tar-years were calculated. More than 99% of the men in the first cohort and 98% of the men in the second cohort were traced. Of the 1,539 men in cohort I who were deceased as of December 31, 1977, death certificates were obtained for 1,432 (93%). Of the 92 men in cohort II who were deceased as of December 31, 1977, death certificates were obtained for 80 (87%). The results showed that men in cohort I died of the following causes at approximately the same rate as or less frequently than men of similar age in the Province of Quebec: tuberculosis; circulatory disease; hypertensive heart disease; trauma; leukemia and aleukemia; and malignant neoplasms of the pancreas, genital organs, brain, intestine, and rectum and other abdominal areas. There were no deaths from pneumoconiosis or Alzheimer's disease. Although the observed and expected numbers of deaths in some of the cause-of-death categories were small, men in cohort I died of the following causes more frequently than did men of similar age in the Province of Quebec: respiratory disease; pneumonia and bronchitis; malignant neoplasms (all sites); malignant neoplasms of the stomach and esophagus, bladder, and lung; other malignant neoplasms; Hodgkin's disease; and other hypertensive disease. Mortality from malignant neoplasms of the bladder and lung was meaningfully related to numbers of tar-years and of years of exposure. Exposure-response relationships were less clear for malignant neoplasms of the esophagus and stomach and for other malignancies. Mortality from respiratory disease for men with 21 or more tar-years of exposure was approximately twice that of persons never exposed to tars. The apparent excess of other hypertensive disease was restricted to men never exposed to tars. Malignant neoplasm of the lung was the only cause of death in cohort II that was in excess of that expected at Quebec provincial rates.

135. CANCER AMONG FARMERS. A REVIEW

Blair A, Malker H, Cantor KP, Burmeister L, Wiklund K
Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD 20892.
Scand J Work Environ Health: 11(6):397-407 1985

During the performance of routine tasks farmers may come in contact with a variety of substances, including pesticides, solvents, oils and fuels, dusts, paints, welding fumes, zoonotic viruses, microbes, and fungi. Because some of these substances are known or suspected carcinogens, the epidemiologic literature regarding cancer risks concerning farmers has been reviewed. Farmers had consistent deficits for cancers of the colon, rectum, liver, and nose. The deficits for cancer of the lung and bladder were particularly striking, presumably due to less frequent use of tobacco among farmers than among people in many other occupational groups. Malignancies frequently showing excesses among farmers included Hodgkin's disease, leukemia, non-Hodgkin's lymphoma, multiple myeloma, and cancers of the lip, stomach, prostate, skin (nonmelanotic), brain, and connective tissues. The etiologic factors that may contribute to these excesses in the agricultural environment have not been identified. Detailed, analytic epidemiologic studies that incorporate environmental and biochemical monitoring are needed to clarify these associations. (98 Refs)

136. MORTALITY AMONG WHITE AND NONWHITE FARMERS IN NORTH CAROLINA, 1976-1978

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Dept. of Community and Family Medicine, Duke University Medical Center, Durham, NC.
Am J Epidemiol: 121(3):391-402 1985

Death certificate information identified 9,245 white and 3,508 nonwhite men who died in North Carolina during 1976-1978 and who had been farmers. The distribution of deaths from various causes among these men was compared to that of other male decedents in the state. For both white and nonwhite farmers, proportional mortality ratios (PMRs) were elevated for tuberculosis (whites, 1.6; nonwhites, 1.7), diseases of the skin and subcutaneous tissue (whites, 2.5; nonwhites, 1.5), and external causes (whites, 1.2; nonwhites, 1.1) and were decreased for cancers of the esophagus (whites and nonwhites, 0.5) and large intestine and rectum (whites and nonwhites, 0.7). White farmers had an increased relative frequency of melanoma (PMR = 1.2) and other skin cancer (PMR = 1.8), while nonwhite farmers had an increased relative frequency of melanoma (PMR = 6.3), brain cancer (PMR = 2.3), and leukemia (PMR = 1.5). In addition, among decedents under 65 years of age, both white and nonwhite farmers had an elevated proportional mortality ratio for prostate cancer (whites, 1.6; nonwhites, 1.3). Many of these results are consistent with observations from other studies. Some of these findings, particularly those for nonwhites, warrant further evaluation, including detailed investigation of possibly related farming practices.

137. AGRICULTURALLY RELATED CARCINOGENIC RISK (MEETING ABSTRACT)

Borzsonyi M, Torok G, Pinter A, Surjan A
National Institute of Hygiene, 1966 Budapest, Hungary
Symposium on Role of Cocarcinogens and Promoters in Human and Experimental Carcinogenesis, May 16-18, 1983, Budapest, Hungary Hungarian Cancer Society, 1983.

Carcinogenesis is a multistage process where etiological factors can be regarded as complete carcinogens, initiators or promoters. Despite the rather limited number of definitive human carcinogens, the increasing amount of environmental pollutants might fall in one or other categories of carcinogens. Development in chemical industry resulted in chemisation of agriculture which along with the spread of industrial methods might represent real danger for human being. In this paper we give an account about agricultural chemicals which could play a role in the carcinogenic process. The use of the herbicide 1-naphthylamine may be dangerous because of the presence of bladder carcinogen 2-naphthylamine. Important group of agricultural chemicals have alkylating properties like halogenated hydrocarbons (alkanoles, aryl derivatives, alkan halides etc), which are mutagenic and carcinogenic in animals. Some organophosphate pesticides are also widely used and proved to be genotoxic. Pesticides containing secondary, tertiary and quaternary amino groups could be converted to N-nitroso compounds in vitro and in vivo. We were able to demonstrate in vivo nitrosation of carbamate, morpholine, urea, piperazine and guanidine pesticides, of which N-nitroso derivatives caused tumors in experimental animals. This points to the importance of nitrite and nitrate, present in the environment. The above discussed compounds, having definitive effect in short term genotoxicity tests might endanger human population as initiators or complete carcinogens. Non-genotoxic agricultural chemicals in-

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clude some highly stable, eventually cumulating compounds which either do not induce tumors or increase only the frequency of spontaneous neoplasms. Such group of chemicals is represented mainly by polychlorinated biphenyl pesticides and the TCDD as pesticide contaminant. (no Refs)

138. A PROPORTIONAL MORTALITY STUDY OF THE ACTING PROFESSION

Dupuy RH. Kagey BT. Heid MF
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Am J Ind Med: 8(1):57-66 1985

Proportional mortality of actors and actresses was studied because cancers of many sites have been linked to hair dyes and cosmetics of which actors have been frequent users. Death records (1950-1978) for 2,618 white male and 838 white female members of Actors Equity and the Screen Actors Guild were compared with the U.S. mortality rates. Among males, significantly elevated proportional mortality ratios (PMR) were found for suicide (1.58), cirrhosis of the liver (1.99), all malignancies (1.15), and cancers of the colon/rectum (1.32), pancreas (1.51), and testes (2.37). Colon/rectum and pancrea s cancers were not significantly elevated by proportional cancer mortality. Among females, significantly elevated PMRs were found for suicide (2.02) and lung cancer (2.20). Suicide in either sex was much more common in California than in New York. The elevated lung cancer in females was confined to Equity members. No elevations were found for cancers that have been related to hair dye or cosmetic use - ie, breast, ovary, bladder, leukemia, and lymphomas.

139. CANCER MORTALITY IN LOS ANGELES CITY FIREFIGHTERS (MEETING ABSTRACT)

Lewis SS. Bierman HR. Faith MR
Institute for Cancer and Blood Research, Beverly Hills, CA, 90211
Proc Am Assoc Cancer Res: 24:743 1983

The cancer mortality of firefighters from 1940 to 1980 was investigated. On entry to the Fire Department these 1690 men, 91% of whom were born prior to 1920, were in excellent physical condition. Person-years at risk increased from 2200 in 1940 to 5215 in 1980 concurrent with an increase in personnel. Total person-years at risk exceeded 156,000. The percentage of deaths attributed to cancer from 1945 to 1974 averaged 20.1%; increasing thereafter to over 30%. A comparison of observed number of deaths to that expected in white American males revealed an increase in neoplasm of the brain, prostate, colon and lung. Brain tumors occurred at a rate 120% higher and prostate 116% higher than expected. The potential exposure of firefighters to products of combustion (CO, HCN, Acrolein, Phosgene, etc), toxic spills, a variety of dusts (plaster, asbestos), heavy metals and fumes (exhaust and solvents) which occur unpredictably but repetitively for brief and/or prolonged times emphasizes the hazards of this profession. The multifactorial exposure to immunosuppressants, hematodepressants, carcinogens and their enhancers must all be considered in the development of neoplasms and other disorders in this population. (no Refs)

140. BLADDER CANCER RISK AMONG LAUNDRY WORKERS, DRY CLEANERS, AND OTHERS IN CHEMICALLY-RELATED OCCUPATIONS

Smith EM. Miller ER. Woolson RF. Brown CK
Department of Preventive Medicine. University of Iowa. Iowa City 52242.
J Occup Med: 27(4):295-7 1985

Keywords (MeSH): Adult; Aged; Bladder Neoplasms/*chemically induced; *Carcinogens, Environmental; Female; Human; Hydrocarbons, Chlorinated/adverse effects; Male; Middle Age; Occupational Diseases/*chemically induced; Occupations; Risk; Smoking; Solvents/adverse effects.

141. CARCINOGEN ASSESSMENT OF COKE OVEN EMISSIONS (REVISED DRAFT)

Environmental Protection Agency
Washington, DC
Carcinogen Assessment of Coke Oven Emissions (Revised Draft). Available from National Technical Information Service, Springfield, VA, as PB83-129551:, 217 pp., 1982.

Coke oven workers in Allegheny County, Pennsylvania and at 10 non-Allegheny County coke plants in the United States and Canada were found to be at an excess risk of mortality from cancer of all sites and from cancer of the lungs, bronchus, trachea, kidney, and prostate. An important finding of this study was the dose-response found by both length of exposure and intensity of exposure (top or side of the ovens) for mortality from cancer of the lungs, bronchus, and trachea. A study of Japanese coke oven workers also found them to be at an excess risk of lung cancer mortality. British studies of cancer mortality in coke oven workers have generally been negative, but there were serious weaknesses in these studies. (Author abstract)

142. RISK OF CANCER IN OVEN-BLOCK WORKERS IN CARBONIZATION PLANTS - RESULTS OF A COHORT STUDY

Manz A
Zentralbl Arbeitsmed Arbeitsschutz Prophyl Ergonomie: 34(2):34-41 1984

Keywords (MeSH): Adult; Bladder Neoplasms/*chemically induced; Coal Tar/*adverse effects; English Abstract; Female; Human; Male; Middle Age; Occupational Diseases/*chemically induced; Respiratory Tract Neoplasms/*chemically induced; Risk.

D.
Interrelationship of Smoking with Occupational Exposure

143. TOBACCO SMOKING, COFFEE DRINKING, AND OCCUPATION AS RISK FACTORS FOR BLADDER CANCER IN GREECE

Rebelakos A. Trichopoulos D. Tzenou A. Zavitsanos X. Velonakis E. Trichopoulos A
Department of Hygiene and Epidemiology, University of Athens Medical School, Goudi, Greece.
JNCI: 75(3):455-61 1985

Patients with bladder cancer (250 males and 50 females), consecutively admitted during a 2-year period in the major cancer hospital of Athens, and an equal number of age- and gender-matched comparison patients with orthopedic conditions were interviewed regarding demographic, socioeconomic, and biomedical characteristics, including their occupations and their use of coffee and tobacco prior to the onset of their present disease or condition. Analyses of the data showed that cigarette smoking is an important, statistically significant and dose-dependent risk factor for bladder cancer, particularly in males (tobacco smoking is rare among older Greek women); drinking 2 or more cups of Greek coffee per day appears to be a risk factor for bladder cancer, independent of tobacco smoking, although the association is neither strong nor dose dependent; and a priori specified 'high-risk' occupations were associated with an increased rate ratio for bladder cancer among men less than 65 years and among women in general but not among older men. The overall results of this study indicate that the established risk factors for bladder cancer in the United States and in other developed

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countries are, apparently, equally important for bladder cancer in Greece, despite the differences in composition and conditions of use of Oriental tobacco and Greek coffee and in the activities and exposures to carcinogens in the Greek work place.

144. COMPARISON OF CRUDE AND SMOKING-ADJUSTED STANDARDIZED MORTALITY RATIOS

Blair A. Hoar SK. Walrath J
Environmental Epidemiology Branch. National Cancer Institute. Bethesda. MD 20892
J Occup Med: 27(12):881-4 1985

To systematically evaluate bias in estimating relative risks associated with occupational exposures obtained in the absence of smoking data, the authors compared crude and smoking-adjusted standardized mortality ratios for selected occupations using data from a study of U.S. veterans. Crude and smoking-adjusted SMRs were highly correlated: lung cancer (r = .88), bladder cancer (r = .98), and intestinal cancer (r = .97). Greater differences occurred for lung cancer, which is more strongly related to smoking than bladder or intestinal cancer.

145. BLADDER CANCER AND SMOKING IN MALES: TYPES OF CIGARETTES, AGE AT START, EFFECT OF STOPPING AND INTERACTION WITH OCCUPATION

Vineis P. Estere J. Terracini B
Unit of Cancer Epidemiology. Main Hospital and University of Turin. Italy.
Int J Cancer: 34(2):165-70 1984

A case-control study of 512 male cases of bladder cancer and 596 male hospital controls (all living in the province of Turin, Northern Italy) has been analyzed for cigarette smoking. Relative risks (RRs) decreased with years since stopping, whereas they seemed not to change with age starting to smoke. A multiplicative effect of RRs for smoking and high-risk occupations was suggested. Filters exerted a protective effect (RR = 0.3 for smokers of filter-tip cigarettes only vs. smokers of non-filter-tip cigarettes). A previously unreported difference was noticed between black types and blond types of tobacco (RR = 0.4 for smokers of the blond types only vs. smokers of the black types, adjusted for age, average daily amount, years since stopping, occupation and use of filter).

146. OCCUPATIONAL BLADDER CANCER AND CIGARETTE SMOKING IN WEST YORKSHIRE

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Scand J Work Environ Health: 8(Suppl1):79-82 1982

Results of the preliminary analysis of the first 1,000 cases of bladder cancer pooled from three hospital districts, Huddersfield with both high mortality and morbidity, Bradford with high morbidity and low mortality, and Wakefield with both low morbidity and mortality, are presented. All cases prevalent at the onset of the study in 1978 together with all incident cases occurring since, up to 1980 were included. All prevalent cases were matched with one hospital referent and all incident cases with two. The following information was collected: identification, coffee and alcohol drinking habits, smoking habits, saccharin use, past medical history, past drug treatment, occupational history, hobbies, and family history. Results of the analysis for cigarette smoking showed a statistically significant risk for bladder cancer. The risks associated with the cases that had worked for at least 6 mo in seven risk occupations are summarized. The chemical industry workers included a preponderance of process workers in the dye manufacturing industry. Summary of the risk ratios for contemporaneous smokers and nonsmokers in three occupations is presented. The differences between the pair of risk ratios were statistically significant for dye manufacturers but not for dye users or printers. The age of workers at the beginning of work in the dye manufacturing industry influenced the subsequent risk of developing bladder cancer. The actual length of employment and the date of beginning the work were both important variables. (11 Refs)

147. CANCER RISKS AMONG WOODWORKERS: EVIDENCE OF INTERACTION WITH CIGARETTE SMOKING (MEETING ABSTRACT)

Stellman S. Garfinkel L
American Cancer Society. New York. NY. 10001
Am J Epidemiol: 116(3):585 1982

A total of 417,120 men in 25 states were enrolled in a prospective study in 1959 and followed for 12 years. Of these, 10,322 listed their usual employment in woodworking trades, such as carpentry or lumber industry. During the 12 years of follow-up, 2503 woodworkers (24.2%) and 84,841 non-woodworkers (20.9%) died. Standardized mortality ratios (SMRs) were calculated for various causes of death among woodworkers, with expected deaths based upon age-specific death rates in non-woodworkers. Mortality ratios for all causes of death and for all sites of cancer combined were near unity. Stomach cancer was higher among woodworkers (SMR = 152), and particularly among carpenters (SMR = 177). Elevated rates were found for cancers of the lung, bladder, skin, malignant melanoma, and leukemia (though not for Hodgkin's disease as previously reported by others). Woodworkers had lower rates of colon-rectum cancer, lymphoma, and coronary heart disease. There were two woodworker deaths from nasal cavity cancer (0.9 expected). Higher rates of lung and bladder cancer in woodworkers who smoked similar amounts suggest the possibility of an interaction between woodworking-associated exposures and cigarette smoking which merits further investigation. (no Refs)

148. GASOLINE EXPOSURE, SMOKING, AND KIDNEY CANCER [LETTER]

Domiano SF, Vena JE, Swanson MK
J Occup Med: 27(6):398-9 1985

Keywords (MeSH): Adult; Aged; Gasoline/*adverse effects; Human; Kidney Neoplasms/*chemically induced; Male; Middle Age; Occupational Diseases/*chemically induced; Petroleum/*adverse effects; Risk; *Smoking.

E.

Reviews on the Etiology and Epidemiology of Potential Occupational Cancer of the Urinary Tract and the Prostate

149. ETIOLOGY OF BLADDER CANCER

Di Silverio F. Bizzarri M. Chiappini L. Ottaviano C. Tenaglia R
Universita. La Sapienza. Roma Cattedra di Patologia Urologica.
Minerva Med: 76(14-15):691-704 1985

Multiple agents have been suggested as urinary bladder carcinogens. Of these, certain aromatic amines and some tryptophan metabolites (Anthranilic acid, 3 hydroxy Anthranilic acid) have been proved to be carcinogenic. Others are suggested but are not conclusively proved as carcinogenic agents. Various animal species have been used as experimental models for the study of induction of cancer of the bladder and substantial progress has been made in the search for etiologic factors and pathogenesis of bladder tumors. A carcinogenic model of cancer bladder induction is proposed.

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However, knowledge of the tumorigenesis of cancer of the bladder is still limited and fragmentary. It appears, however, that Tryptophan dysmetabolism play a major role in this field and future experimental and epidemiologic studies should take this fact into consideration.

150. ADVANCES IN THE ETIOLOGY OF UROTHELIAL CANCER

Morrison AS

Department of Community Health, Brown University, Providence, Rhode Island.

Urol Clin North Am; 11(4):557-66 1984

Cigarette smoking has been shown to be the most important known preventable cause of bladder cancer. Occupations have continued to come under suspicion, although many of the newer findings are tentative. Neither coffee drinking nor use of artificial sweeteners appears to have been responsible for much, if any, human bladder cancer

151. REVIEW: PROSTATE CANCER EPIDEMIOLOGY

Flanders WD

Department of Epidemiology, University of Alabama, Birmingham.

Prostate; 5(6):621-9 1984

Prostate cancer is common among men in the United States. Factors of possible importance in the etiology of prostate cancer include diet, primarily implicated by ecologic studies of national, regional, and ethnic variation in rates; endocrine function, implicated by the importance of endocrine function in normal prostatic growth and in the treatment of prostate cancer; genetic susceptibility, supported by familial aggregation; some aspect of sexual behavior, suggested by case-control differences in sexual behavior; and occupational exposure, particularly cadmium exposure. Despite the public health importance of prostate cancer, it has received only moderate epidemiologic study; thus the etiologic importance of these and other possible determinants of prostate cancer risk is uncertain [55]. (73 Refs)

152. BLADDER CANCER - A CONSEQUENCE OF INDUSTRIALIZATION?

Gericke D. Harzmann R

Fortschr Med; 104(3):33-7 1986

Keywords (MeSH): Bladder Neoplasms/*chemically induced; English Abstract; Female; Human; *Industry; Male; Occupational Diseases/*chemically induced; Risk.

153. THE WORK-RELATEDNESS OF RENAL DISEASE (50 Refs)

Landrigan PJ. Goyer RA. Clarkson TW. Sandler DP. Smith JH. Thun MJ. Wedeen RP

Arch Environ Health; 39(3):225-30 1984

Keywords (MeSH): Analgesics/adverse effects; Animal; Cadmium Poisoning/complications; Disease Models, Animal; Human; Kidney Failure, Chronic/*chemically induced; Kidney Neoplasms/*chemically induced; Kidney/drug effects; Lead Poisoning/complications; Occupational Diseases/*chemically induced; Review ; Solvents/poisoning.

154. OCCUPATIONAL BLADDER CANCER

Hansen KS. Jensen AA

Ugeskr Laeger; 146(44):3393-8 1984

Keywords (MeSH): Animal; Bladder Neoplasms/*etiology/occurrence; Dogs; English Abstract; Human; Occupational Diseases/*etiology/occurrence; Risk.

155. EPIDEMIOLOGY OF KIDNEY CANCER

Dayal H. Kinman J

Statistical Laboratory, Fox Chase Cancer Center, Philadelphia, Pa.

Semin Oncol; 10(4):366-77 1983

Renal-cell carcinoma usually affects those over 40 years old, and, in any age group, the disease occurs about twice as frequently among men as it does among women. The incidence of the disease has been steadily increasing over the years. In the United States, the probability of surviving after diagnosis of renal cancer has been improving since 1940 regardless of race, sex, and age at diagnosis. The relationship between SES and the chance of developing the disease is sporadic with an indication of a slightly higher risk in the upper socioeconomic classes. Urban/rural comparisons consistently suggest that a higher risk is associated with urban residence. Tobacco use is probably the only environmental factor that could be considered to be etiologically related to cancer of the kidney. A variety of studies point to a moderate but consistent association with tobacco use in the form of cigarette, cigar, or pipe smoking. The excess of the disease in males compared to females and the lower incidence in Mormons may partly be due to the confounding effect of smoking. Dietary vitamin A or vitamin A supplements may have an antipromoting effect in the development of kidney cancer. Hypotheses implicating fat and/or cholesterol intake in the etiology of cancer of the kidney appear to be too tenuous. The evidence of a relationship between concentrations of certain trace metals in drinking water and incidence of renal cancer is weak. Similarly, there is no strong indication of an increased risk among individuals exposed to radiation. In general, with the exception of the observation of an unusually high risk among coke-oven workers, occupational studies have not identified any high-risk groups. Familial aggregation, though rare, occurs with peculiar disease characteristics that may predict similar cancers in the proband's relatives with a high degree of accuracy. In conclusion, the etiology of cancer of the kidney is poorly understood. The descriptive epidemiology of the disease provides some interesting insights into the correlates of the distribution of the disease.(ABSTRACT TRUNCATED AT 400 WORDS)

156. UROLOGIC CANCER II - CANCER OF THE BLADDER

Srougi M. De Goes GM

Universidade de Sao Paulo, Sao Paulo, Brasil

J Bras Urol; 9(2):78-87 1983

In this review article, the authors discuss the epidemiology and etiology, clinical aspects, and treatment of bladder neoplasms. They review the contribution of occupational factors, exposure to aromatic amines, smoking, artificial sweeteners and tryptophan metabolites to its occurrence. Clinically, 70% of patients (pts) present with hematuria as the initial symptom, and 25% present with symptoms of bladder irritation. Treatment planning must be based on the stage of the lesion, histological grade and the presence of carcinoma in situ. Other factors to be considered are: lesion morphology, presence of ABO antigens on the tumor surface and chromosomal complement of the neoplastic cells. The authors review surgery, combination chemotherapy, immunotherapy and radiotherapy of bladder neoplasms with specific reference to superficial and low-grade tumors, deep infiltrative and high grade tumors and metastatic lesions. Various protocols are described. (82 Refs)

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157. BLADDER CANCER

Glashan RW

Royal Infirmary, Huddersfield, West Yorkshire, England

Practitioner; 226(1373):1891-1894,1896,1898 1982

Etiological factors, histopathology, staging, clinical presentations and investigations, and treatment of bladder cancer are reviewed. Men are affected three times more commonly than women, the incidence increasing with age. Certain aromatic amines, such as naphthylamine and benzidine, are carcinogenic to the human bladder. The predominant symptom of bladder cancer is hematuria which characteristically is painless. Treatment consists of cystectomy and chemotherapy. Removal of the bladder is a major surgical procedure with a small mortality but high morbidity rate. (4 Refs)

158. INDUSTRIAL BLADDER CANCER

Glashan RW

Consultant Urologist, Royal Infirmary, Huddersfield HD3 3EA, England

Br Med J; 284(6316):614-615 1982

Incidence, history, industrial screening, and compensation for occupational bladder cancer are discussed. Past research indicated that exposure to benzidine, beta- or alpha- napthylamine increased the risk of dying from bladder cancer. Regular screening of workers is recommended since reversal of early cases is possible with intravesical doxorubicin therapy. Legislation to compensate workers who develop bladder cancer should be revised to include compensation for early disease, since carcinoma in situ usually occurs before the actual development of a tumor, and to include more people. (17 Refs)

159. EPIDEMIOLOGY OF TUMORS OF THE URINARY BLADDER

Bollack C, Goldschmidt P, Schaffer P

Hospices civils, F-67005 Strasbourg Cedex, France

Helv Chir Acta; 49(3/4):285-292 1982

The epidemiological and etiological aspects of carcinoma of the urinary bladder are reviewed. Bladder carcinoma, the most frequent neoplasm of the urinary tract, is most frequent among elderly men. Its incidence is especially high in the chemical and dye industries, and in areas with endemic schistosomiasis. Smoking was also recognized as a factor of bladder carcinoma, while coffee consumption, analgesics, and air pollution are of secondary importance etiologically. The etiological role played by saccharin cannot be proved or disproved because of the long latent period of the tumor (17-30 yr). (40 Refs)

160. TUMOURS OF THE URINARY BLADDER, RENAL PELVIS, URETER AND URETHRA

Althoff J, Chesterman FC

Department of Experimental Pathology, Hanover Medical School, Federal Republic of Germany

IARC Sci Publ; (34):163-8 1982

Keywords (MeSH): Animal; Bladder Neoplasms/chemically induced; *Carcinogens; Comparative Study; Diethylstilbestrol; Hamsters; Human; Kidney Neoplasms/chemically induced; Kidney Pelvis; Mesocricetus; Neoplasms, Experimental/chemically induced/pathology; Ureteral Neoplasms/chemically induced; Urinary Tract/anatomy and histology; Urologic Neoplasms/*chemically induced/pathology; 2-Acetylaminofluorene.

161. ASSOCIATION OF FATHER'S OCCUPATION AND CANCER IN CHILDREN

Terracini B, Pastore G, Segnan N

University of Torino, Italy

Biol Res Pregnancy Perinatol; 4(1):40-5 1983

Seven epidemiologic studies on the possible association between parental occupations and cancer in childhood were reviewed. Most were based on the hypothesis of an etiologic role of parental occupations, involving exposure to the broad category of 'hydrocarbons'. The relevant observations were contradictory, possibly because of the vagueness of the definition of the risk factor. Some findings were significant in at least two studies, such as an excess of machinists and mechanics among fathers of children with Wilms' tumor and an excess of occupations with exposure to paints among children with brain cancer. These and other findings should be considered as hypotheses for further studies.

162. CHEMICALLY INDUCED RENAL PAPILLARY NECROSIS AND UPPER UROTHELIAL CARCINOMA. PART 1

Bach PH, Bridges JW

Robens Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, England

CRC Crit Rev Toxicol; 15(3):217-329 1985

In the past, renal papillary necrosis (RPN) has been commonly associated with long-term abusive analgesic intake, but over recent years a wide variety of industrially and therapeutically used chemicals have been shown to induce this lesion experimentally or in man. Destruction of the renal papilla may result in: (1) secondary degenerative cortical changes which precede chronic renal failure or (2) a rapidly metastasizing upper urothelial carcinoma, which has a very poor prognosis. This article will briefly review the published data on the morphology, function, and biochemistry of the normal renal medulla and the pathology associated with RPN, together with the secondary changes which give rise to cortical degeneration or epithelial carcinoma. It will then examine in detail those chemicals which have been reported to cause RPN in an attempt to delineate structure-activity relationships. Finally, the many different theories that have been proposed to explain the pathophysiology of RPN will be examined and an hypothesis will be put forward to explain the primary pathogenesis of the lesion and its secondary consequences. (795 Refs)

163. CHRONIC KIDNEY DISEASE AND ORGANIC CHEMICAL EXPOSURES: EVALUATIONS OF CAUSAL RELATIONSHIPS IN HUMANS AND EXPERIMENTAL ANIMALS

Kluwe WM, Abdo KM, Huff J

National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

Fundam Appl Toxicol; 4(6):889-901 1984

Chronic renal failure is a serious health problem in the United States and other developed countries, and large amounts of public funds are being expended for what is essentially palliative treatment of this disease. Historical data also indicate increasing trends for urinary tract cancers of both sexes in the United States. Although the data on humans are not definitive, causal associations appear to exist between occupational exposures to some hydrocarbon solvents and chronic kidney disease, and there is preliminary evidence that suggests an association between organic chemical exposures and cancers of the urinary tract in humans. A review of more than 230 chemicals tested in two-year chronic toxicity studies by the National Toxicology Program (NTP)/National Cancer Institute (NCI) has identified two chemical

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classes that commonly produced nonneoplastic chronic renal disease in rodents: aromatic amines and organohalides. Tumors of the kidney were most frequently produced by alkyl or alkenyl halide compounds, while tumors of the bladder were caused by aromatic amines. Consistent with many literature reports, short-chain halogenated hydrocarbons appeared to have a propensity for causing a low incidence of renal tubular carcinoma in exposed rodents. Comparative analyses of the NTP/NCI studies did not indicate consistent sex or species differences in the nonneoplastic chronic toxic response, but chemically induced urinary tract cancers occurred more commonly in rats than in mice, and chemically induced cancers of the kidney occurred more commonly in males than in females. Viewed collectively, these data indicate a potential for organic chemicals, especially halogenated hydrocarbons and aromatic amines, to produce chronic kidney injury in humans and other mammalian species.(ABSTRACT TRUNCATED AT 250 WORDS) (58 Refs)

164. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER

Louer GM

Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706

Cancer; 49(5):1056-1066 1982

A significant portion of the incidence of human urinary bladder cancer can be attributed to occupational and cultural (tobacco smoking) situations associated with exposures to various arylamines, many of which represent established human carcinogens. A brief historical overview of research in bladde r cancer causality indicates that the identification of causal agents and causal mechanism has been approached and rests upon information gathered at the organismal (geographical/historical), cellular, and molecular levels of biologic organization. This viewpoint speaks of a natural evolution within the biomedical sciences; a natural evolution from descriptive approaches to mechanistic approaches; and a natural evolution from more or less independent discipline-oriented approaches to hierarchically organized multidisciplinary approaches. Available information relevant to bladder cancer causality can be readily integrated into general conceptual frameworks to yield a hierarchial view of the natural history of urinary bladder cancer, a view consistent with contemporary natural systems and information theory and perhaps relevant also to other chemically induced epithelial cancers. Such frameworks are useful in appreciating the spatial and temporal boundaries and interrelationships in causality and the conceptual interrelationships within the biomedical sciences. Recent approaches in molecular epidemiology and the assessment of relative individual susceptibility to bladder cancer indicate that such frameworks are useful in forming hypotheses. (Author abstract) (62 Refs)

165. AN EVALUATION OF THE SIGNIFICANCE OF EXPERIMENTAL HYDROCARBON TOXICITY TO MAN

Trump BF, Lipsky MM, Jones TW, Heatfield BM, Higginson J, Endicott K, Hess HB

Dept. of Pathology, Univ. of Maryland Sch. of Medicine, Baltimore, MD 21201

Adv Mod Environ Toxicol; 7:273-88 1984

Papers presented at the Workshop on the Kidney Effects of Hydrocarbons held in Boston, MA in June of 1983 and sponsored by the American Petroleum Institute are reviewed and critically analyzed, and a further evaluation of data available on other hydrocarbons and related compounds is included. Sections within this review have the following headings: review and analysis of the chronic inhalation study (CHIS) of motor fuel (rat kidney, mouse liver); interpretation of renal lesions in the male rat in the CHIS and other related hydrocarbon studies (acute, subacute, and chronic non-neoplastic lesions; chronic, preneoplastic, and neoplastic lesions); interpretation of liver lesions in female mice; species and sex comparison of the development and microscopic anatomy of the kidney; species and sex comparisons of the mixed-function oxidase system in the kidney; old rat nephropathy; review of human kidney lesions related to hydrocarbon exposure; and the relationship between hydrocarbon-induced renal lesions in rodents and humans. The weight of evidence suggests that some component(s) of unleaded gasoline may be relatively weak carcinogens in male rats, perhaps acting as promoters and/or cocarcinogens. The implications of these studies for man cannot be stated at present. Results of epidemi ologic and case-control studies in humans indicate, however, that gasoline exposure at levels experienced in the general population presents little, if any, carcinogenic risk to man. Anatomical, histologic, and physiologic differences between rats and humans may be partly responsible for the apparent differences in renal response. (23 Refs)

166. INHALATION ANESTHETICS, ANTICANCER DRUGS AND STERILANTS AS CHEMICAL HAZARDS IN HOSPITALS

Vainio H

Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland

Scand J Work Environ Health; 8(2):94-107 1982

Occupational health hazards associated with chemicals most frequently used in hospital facilities are reviewed. Properties and occurrence of inhalation anesthetics are discussed. Operating room staff have an increased risk of spontaneous abortion with high concentrations of nitrous oxide being the causative factor. Evidence that inhalation anesthetic gases cause increased cancer risk among exposed persons is still fairly limited. Some of the anesthetic agents are, however, known to be mutagenic in various test systems. Therefore special attention should be paid to the epidemiologic surveillance of persons exposed to anesthetic agents. The relationship of inhalation anesthetics to liver, CNS, and kidney diseases and other health hazards is discussed. The mutagenicity, carcinogenicity, and teratogenicity of anticancer drugs are discussed. Liver damage and occupational health hazards associated with cancer chemotherapy agents are considered. Chemical sterilants, such as ethylene oxide (EO) and formaldehyde (FM), have been shown to be mutagenic in several test systems. In animal experiments, EO has been related to mononuclear leukemia, peritoneal mesothelioma, and sarcomas. It is recommended that exposure to EO by hospital employees be minimized. FM has been related to the development of nasal squamous cell tumors in rats. Other health effects of chemical sterilants are discussed. Health effects of antimicrobial agents, such as hexachlorophene and propylene oxide, are discussed. (92 Refs)

167. CARCINOMA OF THE RESPIRATORY TRACT AFTER OCCUPATIONAL EXPOSURE TO TAR: A CRITICAL OMISSION FROM THE LIST OF OCCUPATIONAL DISEASES

Manz A

Monckebergstrasse 8, im Hause der HWW, D-2000 Hamburg 1, W. Germany

Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(4):118-127 1982

Current lists of occupational diseases maintained by the Federal Republic of Germany and other European countries attribute only the skin disorders to the occupational exposure

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to coal tar. Exposure is considered to be limited to workers in coke plants. However, other workers, such as road repair crews who use tar, are also exposed. Recognition of occupational hazards affects the practice of occupational medicine, effort at prevention, and measures to humanize the workplace. Legal requirements f or reporting of job-related diseases include mucosal changes or carcinogenesis in the urinary bladder as a criterion. Since anthracite coal tar and pitch contain compounds such as beta-naphthylamine, workers exposed to these substances should be covered by appropriate regulations. However, the presence of known carcinogens in coal tar and pitch is apparently not widely known. Studies in several countries have shown an increased incidence of cancers of the respiratory tract and urinary bladder among gasworks employees when compared to nonexposed workers such as office workers and water works employees. Smoking apparently affects the incidence of cancers among nonexposed workers but not among exposed workers. Current evidence therefore indicates that respiratory and bladder cancers should be included on the lists of occupationally related diseases. (61 Refs)

168. THE CARCINOGENIC POTENTIAL OF BENZIDINE-BASED DYES

Gregory AR
Consumer Product Safety Commission, Bethesda, Maryland.
J Environ Pathol Toxicol Oncol: 5(4-5):243-59 1984

Keywords (MeSH): Animal; Benzidines/adverse effects/metabolism/*toxicity; Bladder Neoplasms/chemically induced; *Carcinogens; Chemistry, Physical; Colonic Neoplasms/chemically induced; Dyes/adverse effects/metabolism/*toxicity; Human; Liver Neoplasms/chemically induced; Occupational Diseases/chemically induced; Risk-Taking; Time Factors.

169. CARCINOGENIC RISK OF NEOZONE D (N-PHENYL-2-NAPHTHYLAMINE) (16 Refs)

Pliss GB, Zabezhinskii MA
Vopr Onkol: 29(7):91-3 1983

Keywords (MeSH): Animal; Biotransformation; Bladder Neoplasms/chemically induced; Chemical Industry; Dogs; Female; Human; Male; Mice; Naphthalenes/*toxicity; Neoplasms/*chemically induced; Neoplasms, Experimental/chemically induced; Occupational Diseases/chemically induced; Rats; Review; 2-Naphthylamine/analogs and derivatives/metabolism/*toxicity.

II.

CARCINOGENICITY STUDIES OF OCCUPATION-RELATED CHEMICALS PURPORTED TO CAUSE URINARY TRACT OR PROSTATE CANCER

A.

Carcinogenicity Studies Involving Aromatic Amines

170. CHRONIC TOXICITY AND CARCINOGENICITY STUDIES OF GENTIAN VIOLET IN MICE

Littlefield NA, Blackwell BN, Hewitt CC, Gaylor DW
Department of Health and Human Services, Food and Drug Administration, Jefferson, Arkansas 72079.
Fundam Appl Toxicol: 5(5):902-12 1985

Gentian violet is a dye belonging to a chemical class known as the di- and triaminophenylmethanes. Although it has been used for many years for the control of fungal and intestinal parasites, for various uses in veterinary medicine, and as an additive to the feed of chickens to inhibit propagation of mold and fungus, very few long-term toxicity data are available. A life span dosing study of gentian violet in the diet of 720 males and 720 females of B6C3F1 mice (C57BL/6 X C3H) at dose levels of 0, 100, 300, and 600 ppm was done to determine its toxicity and carcinogenicity. Sacrifices were conducted after 12, 18, and 24 months of continuous dosing. There was no effect on food consumption or body weight gain; however, a dose effect was noted for mortality rates. Mortality (adjusted for sacrifices) in the controls of both sexes was less than 15% at 24 months, but was approximately 64% in the females and 23% in the males given the high dose. Females appeared to be more susceptible than males. A positive dose response for hepatocellular carcinoma was noted in males at 24 months and in females at 18 and 24 months. Statistical tests for dose-related trends with respect to mortality due to liver neoplasms, prevalence of liver neoplasms, and time to onset of liver neoplasms showed positive trends in both males and females. Other dose-related toxicological responses, particularly in the female mice, included erythropoiesis in the spleen, atrophy of the ovaries, adenoma of the Harderian gland, and the presence of type A reticulum cell sarcomas in the urinary bladder, uterus, ovaries, and vagina. The estimation of risk of 10(-6) over background for malignant liver neoplasms using linear extrapolations showed a lower bound on the virtually safe dose (VSD) to be 2 ppb for the female mice and 1 ppb for the male mice. For benign and malignant liver tumors together, the lower bound on the VSD was essentially the same as for malignant liver neoplasm alone. Under the conditions of the experiment described above, gentian violet appears to be a carcinogen in mice at several different organ sites.

171. CARCINOGENIC AROMATIC AMINES AND RELATED COMPOUNDS

Garner RC, Martin CN, Clayson DB
Univ. of York, Cancer Research Unit, York, Y01 5DD, England
ACS Monogr: (182):175-276 1984

Unlike the polycyclic aromatic hydrocarbons, aromatic amines do not induce tumors at the site of their administration but usually at a distant site such as the liver, intestine, or urinary bladder. Similarly, the response to aromatic amines is specific; 2-naphthylamine, for example, is a potent bladder carcinogen in humans and dogs but is virtually noncarcinogenic in rabbits. These differences lead to the concept that the aromatic amines need metabolic activation to induce tumors. On present evidence, N-hydroxylation is a prerequisite for carcinogenicity of this group of compounds; this reaction may be followed by esterification of the hydroxyl group in some, but probably not in all, cases. The final intermediate is unstable and breaks down to an electrophile that interacts with the tissues. The mechanism of action of some aromatic amines is discussed, certain structural features important for carcinogenicity are shown, and some of the known activation steps for some laboratory animal carcinogens are described. The carcinogenic potentials of the many aromatic amines that have been tested for their ability to induce cancer are discussed. The different molecular types discussed all a re metabolically activated to aryl hydroxylamines or related compounds. In compiling data on those compounds that have been shown to be carcinogenic, results have been eliminated for which insufficient numbers of animals were used and those for which the investigators failed to maintain the animals for enough time to develop tumors; furthermore certain techniques and types of tumors, such as local sarco-

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mas formed in response to the sc injection of some test substances and bladder tumors after bladder implantation, present difficulties in interpretation. What remains demonstrates the major groups of active compounds so far identified. To protect workers from exposure to carcinogens, the suspect compound can now be screened quickly and cheaply using short-term tests for carcinogenicity. (419 Refs)

172. CARCINOGENICITY OF N-PHENYL-1-NAPHTHYLAMINE AND N-PHENYL-2-NAPHTHYLAMINE IN MICE

Wang HW, Wang D, Dzeng RW

Shanghai Institute of Cell Biology, Academia Sinica, China.

Cancer Res; 44(7):3098-100 1984

Technical N-phenyl-1-naphthylamine (PANA), which is an optic isomer of N-phenyl-2-naphthylamine (PBNA), has been used as a rubber additive without suspicion of its being carcinogenic. When male ICR mice were given repeated s.c. injections of both technical and pure PANA in dimethyl sulfoxide, it resulted in high percentage of malignant tumors similar to that in mice given technical PBNA. PANA had a tendency to induce hemangiosarcoma. Similar injections of PANA and PBNA into male TA-1 mice gave similar results. Previous unilateral nephrectomy enhanced both PANA and PBNA induction of renal hemangiosarcomas. The similar carcinogenic potency of PANA and PBNA suggests other routes of metabolic activation besides dephenylation for both chemicals in mice.

173. BENZIDINE DIHYDROCHLORIDE: RISK ASSESSMENT

Littlefield NA, Nelson CJ, Gaylor DW

Department of Health and Human Services, National Center for Toxicological Research, Jefferson, Arkansas.

Fundam Appl Toxicol; 4(1):69-80 1984

Benzidine, recognized as a bladder carcinogen in man and as a liver carcinogen in experimental animals, is the chemical basis of as many as 200 commercial dyes. Physiological processes can metabolize these dyes to release benzidine, thereby creating a potential exposure hazard. To assess this hazard, both sexes of F1 hybrid (genetically homogeneous) and monohybrid (genetically heterogeneous) mice from a BALB/c male and C57BL/6 female cross were exposed for their respective lifespans to benzidine dihydrochloride in their drinking water at concentrations of 0, 30, 40, 60, 80, 120, and 160 ppm for males, and 0, 20, 30, 40, 60, 80, and 120 ppm for females. Animals were removed from the study when they were dead or moribund. This study was terminated after 33 months of exposure. Using the endpoint of hepatocellular adenomas and carcinomas, the Armitage Doll multistage model was used to descri be the tumor rates in the experimental dose range and to obtain the upper confidence level on tumor rates. Linear interpolation was used between zero dose and the upper confidence level of the lowest experimental dosage for predicting potential low dose tumor rates. Dose-response effects on body weight, survival, and liver neoplasms were noted in both stocks. For each of the endpoints, the females were more susceptible than males and the F1 (homogeneous) stock was more susceptible than the monohybrid cross (heterogeneous). The calculated virtually 'safe' dose predicted to produce less than one per million F1 female mice with a liver tumor is 0.045 ppb. One part per billion of benzidine dihydrochloride in the drinking water of these mice is estimated to produce liver tumors in less than 2.23 mice per 100,000 population.

174. THE CHRONIC EFFECTS OF MAGENTA, PARAMAGENTA AND PHENYL-BETA-NAPHTHYLAMINE IN RATS AFTER INTRAGASTRIC ADMINISTRATION

Ketkar MB, Mohr U

Dept. Experimental Pathology, Medizinische Hochschule Hannover, Karl-Weichert-Allee 9, 3000 Hannover 61, W. Germany

Cancer Lett; 16(2):203-206 1982

Effects of magenta, paramagenta, and phenyl-beta-naphthylamine administered intragastrically 2x/wk to Sprague-Dawley rats were investigated in a long-term carcinogenicity study. Tumor incidence, latency, and multiplicity, organ distribution and histological types of tumors, as well as survival times are summarized and presented. Macroscopic alterations and microscopic observations were similar in experimental and control rats and were unrelated to treatment. No treatment-associated tumors were observed. (9 Refs)

175. THE INDUCTION OF RAT BLADDER CANCER BY 2-NAPHTHYLAMINE

Hicks RM, Wright R, Wakefield JS

Sch. Pathology, Middlesex Hosp. Medical Sch., Riding House St., London W1P 7LD, England

Br J Cancer; 46(4):646-661 1982

The widely held belief that 2-naphthylamine is not carcinogenic for the rat has been re-examined. Twenty female Wistar rats were dosed by gastric intubation weekly for 57 wk with 2-naphthylamine, 300 mg/kg body wt, in arachis oil and 20 controls were given arachis oil alone. Animals which became moribund were killed during the course of the experiment and the remainder after 100 wk. A 2-naphthylamine-treated animal died at 21 wk; all others survived 57 wk or longer. The urinary tracts of all but two 2-naphthylamine-treated animals, which were found dead and cannibalized, were examined histologically. No neoplastic disease of the urinary tract was present in control animals. In 10 of the 2-naphthylamine-treated rats there was neither neoplasia nor hyperplasia of the urothelium, but 4 of the 18 examined histologically had large, macroscopically visible bladder cancers; 1 of these also had bilateral transitional cell tumors of the kidney calyces and multiple tumors in both ureters. Anothe r animal had bilateral urothelial cancers in the ureters. The histology and ultrastructure of these urothelial cancers were comparable to those of rat transitional-cell carcinomas experimentally induced with other chemical carcinogens. These results, considered in the context both of early and more recently published biochemical studies of 2-naphthylamine metabolism in the rat, support the possibility that production of the active carcinogenic metabolite in this species may be influenced by a pH-dependent, non-enzymic mechanism in the urine, which could account for individual, strain- and diet-related variations in response in the rat. (Author abstract) (51 Refs)

176. COMPARATIVE CARCINOGENICITY OF O-TOLUIDINE HYDROCHLORIDE AND O-NITROSOTOLUENE IN F-344 RATS

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E

Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Cancer Lett; 16(1):103-108 1982

The carcinogenicity of o-toluidine hydrochloride (TOL) and o-nitrosotoluene (NTOL) in F-344 rats was evaluated. Mean weights were somewhat lower in the TOL and NTOL groups than in the control group. The mean daily doses of TOL and of NTOL (administered in the diet) were 0.062 g and 0.051 g, respectively. Food consumption was slightly less in the treated animals than in the animals fed the control

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diet. NTOL was significantly more effective than TOL in inducing hepatomas and bladder papillomas but was less active in the induction of mammary fibroadenomas. Both compounds induced significant numbers of fibromas of the skin and spleen as well as peritoneal tumors. The sc tumors were fibromas or mammary fibroadenomas. The peritoneal tumors were mesotheliomas and low grade spindle cell sarcomas. All invaded deeply into various abdominal organs and the muscular wall of the cavity. Most liver tumors were highly malignant hepatocarcinomas. Two rats displayed enormous multiple metastases of hepatoma tissue to the lungs. Bladder and kidney tumors were of the usual transitional epithelium type. These results suggest that N-oxidation is important in the induction of bladder and liver tumors, while other metabolic conversions may play a role in the induction of other tumor types observed. (15 Refs)

177. THE EFFECTS OF ANILINE, LEAD NITRATE AND SODIUM ALKYL SULFATE ON CHEMICAL CARCINOGENESIS

Litvinov NN, Veronin VM, Kasachkov VI
A. N. Sysin Res. Inst. Communal Hygiene USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(7):36-39 1982

The effects of treatment with aniline, lead nitrate and sodium alkyl sulfate on NDMA - induced experimental tumors were investigated in 250 noninbred albino rats. After aniline the number of tumor-bearing animals increased by 29.1%. Lead nitrate treatment induced mostly renal carcinoma, while the experiments with sodium alkyl sulfate were inconclusive. (Author abstract) (12 Refs)

178. DOSE-RESPONSE RELATIONSHIP IN THE INCIDENCE OF URINARY BLADDER CARCINOMA IN MICE BY IMPLANTING PELLETS CONTAINING A CHEMICAL CARCINOGEN

Hashida C, Koike N, Nagayama K, Suzuki T, Akiyama I, Takemura N
Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan
Sangyo Igaku; 24(2):186-187 1982

Female ddy-strain mice were given urinary bladder implantations of wax pellets containing 0.3, 0.5, 3.0, 5.0, 10.0, or 12.5% 2-amino-1-naphthol (2A1N). The mice were sacrificed 40 wk later, and the bladder tissues were stained and examined. Survival rates of the rats decreased with increasing concentrations of the 2A1N. All of the tumors occurring in the mice were transitional cell carcinoma, and the incidence of tumor occurrence increased with increased concentration of the 2A1N, indicating a dose-response relationship. Mice administered 5.0% or higher concentrations of the 2A1N had significantly higher rates of tumor occurrence than the control mice. (6 Refs)

179. PRODUCTION OF UNSCHEDULED DNA SYNTHESIS (UDS) IN UROTHELIUM BY URINARY METABOLITES OF ARYLAMINES (MEETING ABSTRACT)

Wang CY, Christensen B, Garner CD, Zukowski K, Lee MS
Michigan Cancer Foundation, Detroit, MI
Proc Am Assoc Cancer Res; 24:291 1983

Hydroxylamines, hydroxamic acids, and their respective N- and O-glucuronic acid conjugates have been suggested to be responsible for the induction of bladder tumors by arylamines. The present study investigated the induction of UDS by these metabolites in cultured urothelial cells of various species. Cultured cells were exposed to the test chemicals in a serum-free medium containing hydroxyurea and 3H-thymidine for 24 hr, and UDS was determined by autoradiography. N-Hydroxy-2-aminofluorene (N-OH-AF), N-hydroxy-2-acetylaminofluorene (N-OH-AAF), the N-glucuronic acid conjugate of N-OH-AF, N-hydroxy-4-aminobiphenyl (N-OH-ABP), N-hydroxy-4-acetylaminobiphenyl (N-OH-AABP), and the N-glucuronic acid conjugate of N-OH-ABP induced UDS in primary cultures of rat, dog, and rabbit urothelial cells, and in 3 normal human urothelial cell lines. The O-glucuronic acid conjugate of N-OH-AAF was not active in these cells. N-OH-AF, N-OH-AAF, N-OH-ABP, and N-OH-AABP were also tested in a primary culture of normal human urothelial cells and all of these compounds were active. These results demonstrate that the urothelial cells of human, dog, rat, and rabbit respond similarly to urinary metabolites of arylamines, and suggest that hydroxylamines, hydroxamic acids and the N-glucuronic acid conjugates may be the active urinary metabolites of arylamines which induce bladder tumors. The O-glucuronic acid conjugates appear to be the detoxified metabolites unless an abnormally high beta-glucuronidase is present in the urine. (no Refs)

180. SPECIES DIFFERENCES IN RESPONSE TO AROMATIC AMINES

Weisburger EK
Laboratory of Carcinogen Metabolism, National Cancer Institute, Bethesda, Maryland.
Basic Life Sci; 24:23-47 1983

Keywords (MeSH): *Amines; Animal; *Carcinogens; Comparative Study; Dose-Response Relationship, Drug; Female; Kidney Neoplasms/chemically induced; Liver Neoplasms/chemically induced; Male; Mice; Mice, Inbred Strains; Neoplasms, Experimental/*chemically induced; *Organ Specificity; Rats; Rats, Inbred F344; *Species Specificity; Structure-Activity Relationship.

B.
Carcinogenicity Studies Involving Biphenyl Compounds

181. CARCINOGENESIS OF 4-AMINOBIPHENYL IN BALB/CSTCRLFC3HF/NCTR MICE

Schieferstein GJ, Littlefield NA, Gaylor DW, Sheldon WG, Burger GT
Department of Health and Human Services, Food and Drug Administration, Jefferson, AR 72079.
Eur J Cancer Clin Oncol; 21(7):865-73 1985

Male and female (840 each) BALB/cStCrlfC3Hf/Nctr mice were given 0, 7, 14, 28, 55, 110 and 220, and 0, 7, 19, 38, 75, 150 and 300 ppm, respectively, of 4-aminobiphenyl in their drinking water. Necropsies on killed animals were performed at 13, 26, 39, 52 and 96 weeks on dose. Dose-related neoplasms were angiosarcomas, bladder urothelial carcinomas and hepatocellular neoplasms. The non-neoplastic dose-related lesions were left atrial thrombosis, bladder urothelial hyperplasia, splenic hemosiderosis and splenic erythropoiesis. The incidences of bladder carcinoma and atrial thrombosis were higher in the males and the incidences of hepatocellular neoplasms and angiosarcomas were higher in the females.

182. RAT PROSTATE AS ONE OF THE TARGET ORGANS FOR 3,2'-DIMETHYL-4-AMINOBIPHENYL-INDUCED CARCINOGENESIS: EFFECTS OF DIETARY ETHINYL ESTRADIOL AND METHYLTESTOSTERONE

Shirai T, Sakata T, Fukushima S, Ikawa E, Ito N
First Department of Pathology, Nagoya City University Medical School.
Jpn J Cancer Res; 76(9):803-8 1985

Twenty consecutive weekly sc injections of 50 mg/kg body weight of 3,2'-dimethyl-4-aminobiphenyl (DMAB), a multi-

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potential carcinogen, were given to male F344 rats and subsequently groups of animals were treated with dietary ethinyl estradiol (EE, 2.5 ppm) or methyltestosterone (MT, 300 ppm) for up to 40 weeks. Prostate carcinomas were found in 4 out of 32 rats given DMAB followed by MT and in 2 out of 29 rats given DMAB alone. Atypical hyperplasia of the prostate epithelium in these two groups was found in 22% and 14%, respectively. Neither carcinoma nor atypical hyperplasia was seen in the prostate of animals given DMAB followed by EE. In other organs, tumors were frequently found in the ear duct, skin, and large intestine and less frequently in the lung, preputial glands, small intestine and liver. EE significantly suppressed tumor incidence of the ear duct and sebaceous glands while increasing the incidence of liver tumor and mesothelioma. The present data indicates DMAB to be a useful carcinogen for the induction of prostate carcinomas in rats.

183. ENHANCING EFFECT OF THIABENDAZOLE ON URINARY BLADDER CARCINOGENESIS INDUCED BY SODIUM O-PHENYLPHENAT E IN F344 RATS

Fujii T, Mikuriya H, Kamiya N, Hiraga K
Department of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan.
Food Chem Toxicol; 24(3):207-11 1986

Sodium o-phenylphenate (OPP-Na), a urinary bladder carcinogen in rats, and another fungicide, thiabendazole (TBZ) were fed separately or simultaneously to F344/DuCrj rats of both sexes. The rats were fed one of six diets, either the basal (control) diet or basal diet containing 0.2% TBZ (group T), 1% OPP-Na (1% SO), 2% OPP-Na (2% SO), 1% OPP-Na plus 0.2% TBZ (1% SO-T) or 2% OPP-Na plus 0.2% TBZ (2% SO-T) for 13 or 65 wk. In the 13-wk study, in which groups of ten rats of each sex were used, urinary bladder tumours appeared in 8/10 males in each of three groups - the 2% SO, 1% SO-T and 2% SO-T groups - but not in the remaining animals. Of these tumours, carcinoma accounted for 3/8 tumours in the 2% SO group, 2/8 in the 1% SO-T group and 8/8 in the 2% SO-T group. In the 65-wk study, in which groups of 15 rats were used, the tumour incidence in males was 1/15 in the T group and 15/15, 12/15 and 14/15 in the 2% SO, 1% SO-T and 2% SO-T groups, respectively, while in the females, tumours were found in 2/15, 1/15 and 12/15 animals in the 2% SO, 1% SO-T and 2% SO-T groups, respectively. Of these tumours, carcinoma accounted for 10/15, 11/12 and 10/14 in the males of the 2% SO, 1% SO-T and 2% SO-T groups, respectively, and for 1/2 and 6/12 in the 2% SO and 2% SO-T females, respectively. The tumour incidences in the 1% SO-T males in the two studies and in the 2% SO-T females in the 65-wk study showed a statistically significant increase over those in the 1% SO males or the 2% SO females. Thus, TBZ apparently enhanced the carcinogenic effects of OPP-Na in the rat urinary bladder.

184. PATHOLOGICAL ANALYSIS OF THE CARCINOGENICITY OF SODIUM O-PHENYLPHENATE AND O-PHENYLPHENOL

Fukushima S, Kurata Y, Ogiso T, Okuda M, Miyata Y, Ito N
First Department of Pathology, Nagoya City University Medical School, Japan.
Oncology; 42(5):304-11 1985

Potential carcinogenicity and promoting effects of sodium o-phenylphenate (OPP-Na) in two-stage urinary bladder carcinogenesis were shown in male F344 rats pretreated with 0.01% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN). However, o-phenylphenol (OPP) did not enhance the occurrence of urinary bladder lesions in rats pretreated with BBN. Scanning electron microscopy of OPP-Na-treated animals demonstrated a dose-dependent production of pleomorphic microvilli on the luminal surface of bladder superficial cells, whereas these were not observed with OPP. These results give some support to the conclusion that OPP-Na may be carcinogenic in the urinary bladder of male rats.

185. SUBCHRONIC TOXICITY STUDY OF SODIUM O-PHENYLPHENATE IN MICE

Shibata M, Hagiwara A, Tamano S, Fukushima S, Ito N
Department of Pathology, Nagoya City University Medical School, Japan.
Toxicol Lett; 25(3):239-46 1985

A 13-week subchronic oral toxicity study of sodium o-phenylphenate (SOPP) was conducted in B6C3F1 mice. Body weight gain was significantly depressed in 1.0 and 2.0% SOPP-treated males and in both sexes treated with 4.0%. Urinalysis showed an increase in pH and a decrease of specific gravity in the 4.0% group of both sexes. Relative liver weights of both sexes receiving 1.0, 2.0 and 4.0% SOPP were significantly greater than those of the controls. No treatment-related histopathologic findings were noted. On scanning electron microscopic (SEM) examination, the bladder epithelium of mice given 2.0% SOPP appeared normal at any time periods investigated. This study showed that while 4.0% SOPP was very toxic to both sexes, 2.0% SOPP did not cause statistically significant changes in organ weights.

186. EFFECT OF LEAD ACETATE ON N-(4'-FLUORO-4-BIPHENYL)ACETAMIDE-INDUCED RENAL CARCINOGENESIS IN THE RAT

Tanner DC, Lipsky MM
Department of Pathology, University of Maryland School of Medicine, Baltimore.
Carcinogenesis; 5(9):1109-13 1984

This study assessed the effect of lead acetate (Pb) on N-(4'-fluoro-4-biphenyl)acetamide (FBPA)-induced renal carcinogenesis. A quantitative investigation was performed to determine the effects of Pb on the numerical density (Nv) and percent volume (%V) of FBPA-induced renal tubular hyperplasia and microscopic nodules. A secondary goal was to evaluate, on a quantitative basis, the role of these putative premalignant lesions in the development of renal carcinoma. Additionally, by quantifying the number per unit area of karyomegalic cells, their relationship to the neoplastic process was examined. Generally, Pb was found to accelerate the onset and development of all renal lesions. Karyocytomegaly did not serve as an indicator of the degree of carcinogenicity of any of the treatment regimens.

187. PROGRESSION OF 4'-(FLUORO-4-BIPHENYL) ACETAMIDE (FBPA)-INDUCED PREMALIGNANT RENAL LESIONS AFTER CESSATION OF EXPOSURE AND NITRILOTRIACETIC ACID (NTA) TREATMENT (MEETING ABSTRACT)

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Department of Pathology, University of Maryland School of Medicine, Baltimore, MD 21201
Proc Annu Meet Am Assoc Cancer Res; 25:151 1984

Dietary exposure to FBPA results in the production of well-defined epithelial lesions in rat kidney. The present study was designed to assess the progression of 'early' renal epithelial lesions after cessation of FBPA exposure and/or their response to subcarcinogenic exposure to NTA. Male, Fischer 344 rats were divided into 10 groups and 7-10 rats from each group were killed after 8, 16, 24, 36, 52 and 62 weeks of control of FBPA (400 ppm) feeding. Additional groups were fed FBPA for 8 or 16 weeks then placed on a control diet for an

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additional 36 to 52 weeks or were given NTA at 1,000 or 2,000 ppm in the water for 36 to 52 weeks. Exposure to FBPA for 8 weeks followed by 36 more weeks on a c ontrol diet resulted in 1/7 rats with renal neoplasms. When NTA was given along with the control diet the renal neoplasm incidence was 7/9 (1,000 ppm) and 3/10 (2,000 ppm). When the time after the 8 week exposure to FBPA was increased to 54 weeks the incidence of renal neoplasia increased in all the groups, ie, control diet, control plus NTA at 1,000 or 2,000 ppm. Feeding FBPA for 16 weeks followed by 36 weeks of control diet resulted in 8/9 rats with renal neoplasia. No neoplasms were noted in the control rats or the rats given 2,000 ppm of NTA alone for 8 to 62 weeks. A similar trend was seen with respect to the incidence of premalignant renal tubule hyperplasia in the same groups. This study demonstrates the ability of altered renal epithelial cells to progress to renal neoplasia, after the cessation of carcinogen treatment. It further suggests that NTA may act as a promoter of renal neoplasia.

188. EFFECTS OF A POLYBROMINATED BIPHENYL MIXTURE IN THE RAT AND MOUSE. II. LIFETIME STUDY

Gupta BN, McConnell EE, Moore JA, Haseman JK
National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
Toxicol Appl Pharmacol; 68(1):19-35 1983

This study was undertaken to characterize the long-term toxic and carcinogenic potential of a polybrominated biphenyl (PBB) mixture in rats and mice of both sexes. Fischer 344 rats and B6C3F1 mice were given 125 po doses of PBB over a 6-month period at 0 (control), 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg body weight/day (5 days/week) and observed for an additional 23 months for rats and 24 months for mice (lifetime observation). The treatments (0.3 mg/kg or higher dosages) shortened the survival time in male rats whereas no such effect was observed in treated females. There was also evidence of shortened survival time in mice treated with 10.0 mg/kg PBB. As observed by uv light, hepatic porphyrin markedly increased at the 6-month observation, then tended to decrease, primarily in mice, following cessation of exposure. Significantly higher incidences of atypical hepatocellular foci, neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas were observed in exposed rats. The incidence of hepatocellular carcinoma was also increased in both male (95%) and female (88%) mice (highest dose level) compared with control male (48%) and female (0%) mice. The incidence of hepatic neoplasms appeared to be dose dependent in both species. Liver tumors were observed primarily in those groups of animals to which PBB was given in doses sufficient to induce readily observable hepatic toxicity. Under the conditions of this experiment, polybrominated biphenyl mixture (Firemaster FF-1) was carcinogenic for Fischer 344 rats and B6C3F1 mice of both sexes. Lesions included neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice. Other manifestations of toxicity included porphyrogenic effects and hepatotoxicity. A significantly higher incidence of chronic progressive nephropathy was observed in male rats of the 1.0, 3.0, and 10.0 mg/kg dosage groups when compared with control males. Gastric ulcers and hyperplastic gastropathy of the glandular portion of the stomach were observed more frequently in male rats, primarily in the high dosage groups.

189. CARCINOGENESIS BIOASSAY IN RATS AND MICE FED DIETS CONTAINING 2-BIPHENYLAMINE HYDROCHLORIDE

Abdo KM, Murthy AS, Haseman JK, Dieter MP, Hildebrandt P, Huff JE
National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
Fundam Appl Toxicol; 2(5):201-10 1982

Diets containing 0.1 or 0.3% 2-biphenylamine hydrochloride were fed to groups of 50 Fischer 344 rats and 50 B6C3F1 mice of each sex for 104-106 weeks. Mean body weights of high-dose rats of both sexes and of low-dose male rats were slightly lower than those of controls. No significant differences in survival times were observed between dosed and control groups. In dosed male rats there was a compound-related increased incidence of kidneys with inflammatory cells and interstitial fibrosis. No tumors in dosed rats were associated with the chemical. Mean body weights of high-dose male mice were slightly lower than those of controls, and survival of high-dose male mice was also significantly (P less than 0.01) reduced relative to controls. Hemangiosarcoma of the circulatory system occurred in female mice with a statistically significant (P less than 0.001) positive trend. The observed incidences of hemangiosarcoma were 0/49 (0%), 1/50 (2%), and 7/50 (14%) in controls, low- and high-dose groups, respectively. In individual group comparisons, the incidence in the high-dose group was significantly (P less than 0.01) higher than that in the controls. The hemangiosarcoma seen in female mice were quite rare with only 6/816 (0.7%) previously seen in controls at the same laboratory and no more than 3 in any group of 50. Hemangiosarcoma also occurred in male mice with a statistically significant positive trend (P = 0.04 by a life table test), with incidences of 0/50 (0%), 2/50 (4%), and 3/50 (6%), in control, low-dose and high-dose groups, respectively. The development of hemangiosarcoma in the high-dose male mice might have been curtailed by the significantly reduced survival time in this group.

190. PROMOTING EFFECT OF SODIUM O-PHENYLPHENATE AND O-PHENYLPHENOL ON TWO-STAGE URINARY BLADDER CARCINOGENESIS IN RATS

Fukushima S, Kurata Y, Shibata M, Ikawa E, Ito N
First Department of Pathology, Nagoya City University Medical School, Mizuho-ku, Nagoya.
Gann; 74(5):625-32 1983

The effects of sodium o-phenylphenate (OPP-Na) and o-phenylphenol (OPP) on 2-stage urinary bladder c arcinogenesis in F344 rats initiated with N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) at levels of 0.01 or 0.05% in drinking water were investigated. Administration of 2.0% OPP-Na in the diet significantly increased both the incidence and the number per 10 cm of basement membrane of preneoplastic lesions (papillary or nodular hyperplasia; PN hyperplasia) of the urinary bladder in rats pretreated with 0.01% BBN, and also those of papilloma and cancer of the urinary bladder in the group pretreated with 0.05% BBN. Moreover, treatment with 2.0% OPP-Na, without prior BBN initiation, induced PN hyperplasia, papilloma and cancer. In contrast, OPP appeared to produce only a slight increase in the incidence of urinary bladder lesions following BBN, and its effect was not statistically significant. It also did not induce tumors of the urinary bladder. These results provide evidence that OPP-Na has promoting activity toward the urinary bladder while OPP does not. Moreover, the possibility that OPP-Na may be a complete carcinogen in the rat urinary bladder deserves consideration.

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191. COMPARATIVE ENHANCING EFFECTS OF POLYCHLORINATED BIPHENYLS AND PHENOBARBITAL ON DIMETHYLNITROSAMINE-INDUCED HEPATIC AND RENAL TUMORIGENESIS IN RATS

Arai M, Hibino T, Takino H, Ouchi N, Hirasawa Y
Department of Pathology, Fujita-Gakuen University, School of Hygiene, Aichi, Japan.
Dev Toxicol Environ Sci; 11:359-62 1983

Keywords (MeSH): Animal; Comparative Study; *Dimethylnitrosamine; Drug Synergism; Kidney Neoplasms/*chemically induced; Kidney/pathology; Liver Neoplasms/*chemically induced; Liver/pathology; Male; Phenobarbital/*toxicity; Polychlorobiphenyl Compounds/*toxicity; Rats; Rats, Inbred F344.

192. AGGLUTINATION ASSAY OF BLADDER CELLS BY CONCANAVALIN A PROVED THE HIGH SUSCEPTIBILITY OF ANALBUMINEMIC RATS TO BLADDER CARCINOGENS

Honma Y, Kahizoe T, Komatsu H, Niijima T, Sugimura T, Nagase S
Urology Division, Mitsui Memorial Hospital, Kandaizumicho, Chiyoda-ku, Tokyo, Japan.
Cancer Lett; 19(1):7-11 1983

The susceptibility of analbuminemic rats, a mutant strain of Sprague-Dawley rats, to bladder carcinogens was examined by testing the agglutinability of isolated bladder epithelial cells by concanavalin A (Con A). One-week treatment with 0.001% N-butyl-N-(4-hydroxybutyl)nitrosamine (BHBN) in the drinking water or 0.01% N-(4-(5-nitro-2-furyl)-2-thiazolyl)-formamide (FANFT), 0.01% and 0.1% 4-aminobiphenyl, 0.1% 4-nitrobiphenyl, 0.1% benzidine, 0.1% 2-naphthylamine or 5% sodium saccharin in the diet clearly induced high agglutinability of bladder cells of male analbuminemic rats but not Sprague-Dawley rats. These results suggest that male analbuminemic rats are very susceptible to bladder carcinogens in general and therefore will be very useful in screening tests for bladder carcinogens.

193. INCREASED AGGLUTINABILITY OF BLADDER EPITHELIAL CELLS BY CONCANAVALIN A IN RATS FED SEVERAL BIPHENYL DERIVATIVES

Honma Y, Kahizoe T, Komatsu H, Niijima T, Sugimura T
Urology Division, Mitsui Memorial Hospital, Chiyoda-ku, Tokyo, Japan.
J Cancer Res Clin Oncol; 106(3):176-8 1983

Biphenyl and its derivatives, 2-aminobiphenyl, 2-nitrobiphenyl, 4-aminobiphenyl, 4-nitrobiphenyl, p-phenylphenol, o-phenylphenol (OPP), and o-phenylphenol sodium salt tetrahydrate (OPP-Na) were examined for their bladder carcinogenicity in rats by a short-term assay for agglutinability of bladder epithelial cells with concanavalin A. Increased agglutinability was observed after 1-week treatment with 2.0% and 1.0% OPP, 2.0% and 1.0% OPP-Na, 0.5 and 0.1% 4-aminobiphenyl, and 0.5% 4-nitrobiphenyl in the diet, suggesting carcinogenicity of these compounds in the bladder. Such an increase in agglutinability was not observed in rats fed diets containing biphenyl, 2-aminobiphenyl, 2-nitrobiphenyl or p-phenylphenol at 2.0%. With OPP-Na, an in vivo carcinogenesis experiment was performed. Bladder carcinomas developed in 14 of 36 male Fisher rats fed a 2% OPP-Na diet for 50 weeks.

194. QUANTITATIVE CYTOTOXICITY STUDIES WITH BLADDER CARCINOGENS IN PROLIFERATING MAMMALIAN UROTHELIAL CULTURES (MEETING ABSTRACT)

Johnson MD, Reznikoff CA, Swaminathan S, Ramirez G, Bryan GT
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 24:243 1983

The objective of this project was to develop a primary cell culture method of mammalian urothelium which could be used for quantitative studies of chemically-induced urothelial carcinogenesis. Explants of epithelium from human ureters and of Fischer 344 rat bladders were isolated by a microdissection technique. Primary outgrowths of epithelial cells were initiated by attachment of explants to type I collagen gels, then replated as single cell suspensions by non-enzymatic dispersion with 0.1% EDTA for up to 3-5 passages. The culture medium consisted of Ham's F12 with 7% fetal calf serum supplemented with 5 ug/ml insulin, 5 ug/ml transferrin and 1 ug/ml hydrocortisone. With this method, proliferating cultures (generation time: 36-48 hr) of tightly adherent, polygonal-shaped urothelial cells were routinely obtained. Light and electron microscopic sections of both primary and passaged cultures demonstrated stratification of the transitional epithelium into 2-3 layers. Apical cells were connected by tight junctions and showed the presence of microvilli and a surface glycocalyx. Numerous desmosomes were observed throughout the cell layers. Using these cultures of human and rat urothelial cells, dose-dependent quantitative responses for cytotoxicity and inhibition of growth rate were demonstrated when cultures were exposed to the bladder carcinogens, nitrosomethylurea and 4-aminobiphenyl. (no Refs)

195. THE ACTIVITY OF 4CMB IN THE BHK CELL-TRANSFORMATION ASSAY

Styles J, Penman S
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 100(1-4):227-228 1982

The baby hamster kidney (BHK) transformation assay was used to study carcinogenic potential of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 2-acetylaminofluorene (2AAF). A positive response was obtained with 4CMB and 2AAF but a negative result was observed with BC. The BHK assay demonstrated that 4CMB is a potent in vitro transforming agent in the absence of S9 mix. BC, a known carcinogen, was negative in the assay, suggesting that 4CMB and BC were tested in a system where the conditions of the test did not reflect those in vivo. (6 Refs)

196. TRANSFORMATION OF BHK 21 C13 CELLS BY BC, 4CMB, AND 4HMB USING THE METHOD OF STYLES

Poole A, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):215-217 1982

Cell-transforming potentials of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) were examined in baby hamster kidney cells growing without attachment in soft agar. 4HMB showed no evidence of cell-transforming potential, whereas 4CMB and BC may possess weak cell-transforming properties. The chemicals were scored as follows: 4HMB negative response, 4CMB unclear response, and BC weak positive response. (2 Refs)

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197. **A COMPARISON OF THE RESPONSE OF BHK21 C13 CELLS TO 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE IN A CELL TRANSFORMATION TEST**
Debnel JM, Daniel MR, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):223-226 1982

Baby hamster kidney 21 C13 cell anchorage-dependent growth, demonstrable as the formation of macroscopically visible colonies after seeding in soft agar, was used to determine the carcinogenic potentials of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB). Transformation frequency and modification of supplementary criteria (dose-response relationship and doubling of number of transformed colonies in treated cultures compared to controls) were used as criteria of positive response. 4HMB satisfied all criteria for a positive response both in the presence and absence of metabolic activation. BC showed some evidence of transforming ability. The response of cells to 4CMB was inconsistent. (7 Refs)

C. Carcinogenicity Studies Involving Azo Compounds

198. **ORGAN-SPECIFIC CARCINOGENESIS IN RATS BY METHYL- AND ETHYLAZOXYALKANES**
Lijinsky W, Saavedra JE, Reuber MD
LBI-Basic Research Program, National Cancer Institute-Frederick Cancer Research Facility, Maryland.
Cancer Res; 45(1):76-9 1985

Azoxyalkanes are isomeric with nitrosodialkylamines and could be similar in their biochemical and bi ological actions. To compare the structure-activity relations in the two series, the tumorigenic activities of four azoxyalkanes, azoxymethane, azoxyethane, Z-ethyl-O,N,N-azoxymethane, and Z-methyl-O,N,N-azoxyethane, were compared in male F344 rats by p.o. administration of 0.54 mM and 0.135 mM solutions in drinking water. In most cases, treatment lasted 30 weeks, but at the higher dose of the two ethylazoxy compounds, 24 weeks of treatment were sufficient. Most of the animals died with tumors that could be attributed to the treatments. The two ethylazoxy compounds caused much earlier death from tumors than the corresponding methylazoxy compounds. All four compounds induced a high incidence of liver neoplasms, which were mainly hepatocellular; the two ethylazoxy compounds also induced a large number of hemangiosarcomas in the liver. At both dose levels, azoxyethane induced tumors of the esophagus and nasal cavity, tumors that were not seen in any other group. Other tumors appearing in significant incidence were in the colon and ileum, induced by azoxymethane and Z-ethyl-O,N,N-azoxymethane, and kidney tumors induced by azoxymethane and Z-methyl-O,N,N-azoxyethane. In F344 rats, azoxyethane was similar in carcinogenic activity to its isomer nitrosodiethylamine, whereas azoxymethane was much less potent than nitrosodimethylamine and induced quite different tumors. These results suggest that the biochemical activation of azoxylkanes is different from the analogous nitrosodialkylamines.

199. **INDUCTION OF TUMORS WITH CYCASIN IN NEWBORN AND PREWEANLING RATS**
Fukunishi R, Kadota A, Yoshida A, Hirota N
Department of Pathology, Ehime University School of Medicine, Japan.
JNCI; 74(6):1275-81 1985

Comprehensive studies of carcinogenesis in newborn or preweanling SD rats were conducted under various dose schedules of cycasin (CAS: 14901-08-7) administration. When cycasin was given sc to newborn rats at day 0, tumors were detected in more than 80% of rats of both sexes; kidney tumors were by far the most common. The incidences of tumors declined in the older groups, namely, over 60% in both sexes in the 7-day group, 55% in males and 8.3% in females in 14-day rats, and 0% in 21-day groups. By multiple administration, tumor incidences elevated considerably. Administration ip of cycasin also gave rise to tumor induction in newborn rats. A total of 435 kidney tumors found in the experiments were studied pathologically. Most of them were classified as mesenchymal tumor; some of them metastasized. A few other tumors were found in the liver and colon.

200. **THE EFFECT OF DEUTERIUM SUBSTITUTION ON CARCINOGENESIS BY AZOXYMETHANE**
Lijinsky W, Reuber MD, Saavedra JE
LBI-Basic Research Program, NCI-Frederick Cancer Research Facility, MD.
Cancer Lett; 24(3):273-80 1984

Azoxymethane was synthesized labeled with deuterium in one or other of the two methyl groups. Groups of 20 male F344 rats were given either 4 mg or 1 mg per week of each of the labeled compounds or of unlabeled azoxymethane each week in drinking water, for 30 weeks, after which the animals were kept until they died. All in the high dose groups died earlier with tumors induced by the treatment than did those in the low dose groups. Azoxymethane itself led to earlier death than either of the deuterium-labeled compounds, and methylazoxymethane-d3 seemed to be the least potent compound. The incidence of liver tumors and of kidney tumors was similar in the groups receiving the same dose of all 3 compounds. However, there were fewer tumors of the colon in animals given methyl-d3-azoxymethane than with the other 2 compounds. These results are consistent with the concept that either methyl group of azoxymethane can be oxidized in the course of activation to a proximate carcinogenic agent for liver, kidney or colon of rats, but that oxidation of the methyl group next to the nitrogen bearing oxygen is more important in the induction of colon tumors.

201. **CARCINOGENICITY OF AZO DYES: ACID BLACK 52 AND YELLOW 3 IN HAMSTERS AND RATS. VOLUME 1**
Plankenhorn LJ
Borriston Labs., Inc., Temple Hills, MD.
Available from National Technical Information Service, Springfield, VA as NTIS/PB84-201136, 240p 1983

The effects of Acid-black-52 (5610640) (AB52) and Yellow-3 (1342296) (Y3) were studied in rats and hamsters. AB52 and Y3 were administered intratracheally to Golden-Syrian-hamsters and Fischer-344-rats once a week for 15 weeks at concentrations of 0.56 to 3.16 milligrams per 0.2 milliliters of saline solution. AB52 and Y3 were administered orally for 27 months, the former at 2 percent and the latter at 0.8 percent in the diet. Animals were observed for clinical symptoms during the experiments. At the end of the experiments, all animals were killed, and complete necropsies and histopathological studies were concluded. AB52 was not found to be oncogenic in either species by either route of administration. Y3 given intratracheally was oncogenic in the adrenal cortex of male hamsters and in the pancreas of male rats. Y3 administered in the diet was oncogenic in the adrenal glands of both sexes of hamsters, in the liver and urinary tract of male rats, and in the endocrine system of female rats. The author concludes that AB52 is noncarcinogenic and Y3 is carcinogenic in rats and hamsters. (Author abstract)

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202. CARCINOGENICITY OF AZO DYES: ACID BLACK 52 AND YELLOW 3 IN HAMSTERS AND RATS. VOLUME 3

Plankenhorn LJ
Borriston Labs., Inc., Temple Hills, MD.
Available from National Technical Information Service, Springfield, VA as NTIS/PB84-201144, 171p 1983

65 Histopathologic data on Golden-Syrian-hamsters and Fischer-344-rats dosed with Yellow-3 (1342296) (Y3) dye were compiled. Animals were given 0.56 to 3.16 milligrams per 0.2 milliliters Y3 intratrac heally in saline solution once a week for 15 weeks, and fed Y3 at 0.8 percent in the diet for 27 months. The organs in the animals of both sexes that were examined were: skin, mammary glands, muscles, salivary glands, mandibular lymph nodes, sciatic nerves, thymus, larynx, thyroid, parathyroid, trachea, bronchus, esophagus, adrenals, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, mesenteric lymph nodes, lungs, liver, gall bladder, spleen, pancreas, kidneys, heart, urinary bladder, cerebellum, cerebrum, pituitary gland, femur, bone marrow, and nasal cavity. Ovaries and uteri were studied in females, and seminal vesicles, prostate gland and testes were studied in males. Data showed that Y3 was oncogenic in the adrenal cortex of male hamsters, and in the pancreas of male rats when administered intratracheally. Y3 given in the diet was oncogenic in the adrenal glands of both sexes of hamsters, in the liver and urinary tracts of male rats, and in the endocrine system of female rats. (Author abstract)

D.

Carcinogenicity Studies Involving Chlorinated or Brominated Hydrocarbons

203. TRICHLOROETHYLENE (TCE) AND PERCHLOROETHYLENE (PERC) INDUCED PEROXISOMAL PROLIFERATION (PP) IN RELATION TO SPECIES AND ORGAN SPECIFIC CARCINOGENICITY (MEETING ABSTRACT)

Goldsworthy TL, Lyght O, Neptun DA, Popp JA
Chemical Industry Inst. of Toxicology, Res. Triangle Park, NC 27709
Proc Annu Meet Am Assoc Cancer Res; 27:73 1986

TCE and PERC cause hepatocellular carcinomas in mice and renal tubular cell adenocarcinomas in rats. Studies were conducted to determine if a relationship existed between PP and the organ/species differences in carcinogenicity. TCE (1000 mg/kg), PERC (1000 mg/kg), trichloroacetic acid (TCA, 500 mg/kg), a metabolite of TCE and PERC, and the potent peroxisome proliferator Wy-14,643 (WY, 50 mg/kg) were administered by gavage to male F344 rats and B6C3F1 mice for 10 consecutive days. TCE, PERC, TCA, and WY increased peroxisomal specific cyanide insensitive palmitoyl CoA oxidation (PCO) in mouse liver (6-, 4-, 3-, 12-fold, respectively, over control). Concurrent administration of TCE and PERC did not induce an additive or synergistic PP response in mouse liver. Only WY (6-fold) and TCA (3-fold) significantly increased rat liver PCO. TCE, PERC, TCA and WY increased PCO in the kidneys of rats (3-, 1.8-, 1.8-, 10-fold) and mice (3.6-, 2.5-, 3-, 7-fold). These results (1) confirm previous observations (Toxicol Appl Pharm 79:365-379, 1985) that TCE causes PP in mouse but not rat liver, (2) demonstrate that PERC administration induces PP in mouse but not rat liver, and (3) support the role of chlorinated hydrocarbon-induced PP in the species specific hepatocarcinogenic response. In contrast, TCE and PERC administration induced PP in the kidney of both rats and mice. The relationship between PP and the renal species specific carcinogenic response of these agents is presently unknown. The lack of correlation between PP and the species specific carcinogenic response in the kidney suggests that other factors are critical. (1 Ref)

204. TOXICOLOGY AND CARCINOGENESIS STUDIES OF TELONE II (TECHNICAL-GRADE 1,3-DICHLOROPROPENE [CAS NO. 542-75-6] CONTAINING 1.0% EPICHLOROHYDRIN AS A STABILIZER) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)

National Toxicology Program
P.O. Box 12233, Research Triangle Park, NC 27709
Natl Toxicol Program Tech Rep Ser; (269):9-10 1985

Toxicology and carcinogenesis studies of Telone II (a soil fumigant containing approx 89% cis- and trans-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% of a trichloropropene isomer, and 1.0% epichlorohydrin) were conducted by administering the commercial-grade formulation in corn oil by gavage to groups of 52 male and 52 female F344/N rats at doses of 0, 25, or 50 mg/kg and to groups of 50 male and 50 female B6C3F1 mice at doses of 0, 50, or 100 mg/kg. Doses were administered three times per week for 104 weeks. Ancillary studies were conducted in which dose groups containing five male and five female rats were killed after receiving Telone II for 9, 16, 21, 24, or 27 months. The primary organs affected were the forestomach (rats and mice), urinary bladder (mice), lung (mice), and liver (rats). Compound-related non-neoplastic lesions included basal cell or epithelial hyperplasia of the forestomach (rats and mice), epithelial hyperplasia of the urinary bladder (mice), and kidney hydronephrosis (mice). Neoplastic lesions associated with administration of Telone II included squamous cell papillomas of the forestomach, squamous cell carcinoma of the forestomach, transitional cell carcinoma of the urinary bladder, alveolar/bronchiolar adenomas, and neoplastic nodules of the liver. Development of lesions in the forestomach (basal cell hyperplasia and squamous cell papilloma) was observed to be time dependent. The results of the scheduled kills supported the findings of the carcinogenesis studies. A data audit was conducted on the Telone II 2-year carcinogenesis studies in rats and mice and the ancillary studies in rats. Except for the already known problem of survival of male vehicle control mice, no other discrepancies or problems that would compromise the validity of the findings or alter the interpretations of these studies were found. Under the conditions of these gavage studies, there was clear evidence of carcinogenicity for male F344/N rats. In female F344/N rats, there was some evidence of carcinogenicity. The experiment in male B6C3F1 mice was considered an inadequate study of carcinogenicity because of the reduced survival in the vehicle control group. However, there was some indication in the male mice of Telone II-related increases of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bron chiolar adenomas and carcinomas of the lung. There was clear evidence of carcinogenicity for female B6C3F1 mice. (56 Refs)

205. A BRIEF REVIEW OF THE TOXICITY AND CARCINOGENICITY OF SELECT CHLORINATED HYDROCARBONS

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Adv Mod Environ Toxicol; 7:141-51 1984

Toxic and carcinogenic actions of chloroform, carbon tetrachloride, hexachlorobutadiene, and related compounds (1,1,2 trichloroethane, hexachloroethane, and 1,2 dichloroethane) in experimental animals are reviewed. The compounds were administered by the oral route (gavage or diet). Mechanisms

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of toxic action, if known, are related to species, strain, and sex differences in target organ response. With regard to carcinogenic action, the chloroform induces renal epithelial neoplasms in male rats, thyroid neoplasms in female rats, and hepatocellular carcinomas in male and female mice. The carbon tetrachloride induces hepatocellular carcinomas in male and female rats or mice and adrenal neoplasms in the mice. The hexachlorobutadiene induces renal epithelial neoplasia in male and female rats. The 1,1,2 trichloroethane induces liver and adrenal tumors in male and female mice; the hexachloroethane, liver tumors in male and female mice; and the 1,2 dichloroethane, liver tumors in male mice, lung tumors in male and female mice, hemangiosarcomas in male and female rats, mammary tumors in female rats, and stomach tumors in male rats. The sites of metabolic activation of the chlorinated hydrocarbons vary (eg, kidney, liver, and thyroid), with quantitative differences in specific enzyme pathways determining toxic versus carcinogenic response. In addition to diversity of initial metabolic site, the diversity of carcinogenic responses may be accounted for by uptake of conjugated metabolites at sites distant from the organ of primary metabolism, followed by transformation to reactive molecules at the site of carcinogenic response. (58 Refs)

206. **CARCINOGENESIS STUDIES OF 1,1,1,2-TETRACHLOROETHANE (CAS NO. 630-20-6) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)**
National Toxicology Program
Box 12233, Research Triangle Park, NC 27709
Natl Toxicol Program Tech Rep Ser No. 237; 146 pp. 1983

Carcinogenesis studies of more than 99% pure 1,1,1,2-tetrachloroethane (TCE) were conducted in groups of 50 male and 50 female F344/N rats and in groups of 50 male and 50 female B6C3F1 mice. The chemical, in corn oil, was administered by gavage to rats at doses of 125 or 250 mg/kg and to mice at doses of 250 or 500 mg/kg. Due to chemically induced toxicity, high-dose mice received the chemical for only 65 wk. Vehicle controls (50 rats and 50 mice of each sex) received corn oil alone. The chemical produced cumulative toxicity with signs of CNS involvement beginning at wk 44; this resulted in significantly lower survival of high-dose male rats ($p=0.001$) and possibly decreased the incidence of late-developing tumors in this group. Mean body wt was similar for dosed and controls rats of either sex. The accidental killing of 27 male and 15 female rats also reduced the sensitivity of the bioassay for detecting a carcinogenic response. Analyzed separately, neither hepatocellular neoplastic nodules nor hepatocellular carcinomas showed a statistically significant increased incidence in male rats. However, the combined incidence of these lesions was significant (p less than 0.05) in life table tests (controls, 0/49, 0%; low-dose, 1/49, 2%; high-dose, 3/48, 6%). A single hepatocellular carcinoma occurred in the high-dose group. The combined incidence of liver tumors in this group was not significant relative to their combined incidence in male vehicle controls in previous studies at the performing laboratory. Kidney mineralization increased in a dose-related fashion in male rats (control, 12/48, 25%; low-dose, 19/50, 38%; high-dose, 26/48. 54%). Mammary gland fibroadenomas occurred with a statistically significant increased (p less than 0.05) incidence in low-dose females, compared with controls (15/49 vs 6/49). Incidence in the high dose group (7/46) was comparable to that in the controls. In female rats, the combined incidence of pituitary adenomas, adenocarcinomas, and carcinomas showed a statistically significant negative trend, and the incidence in the high-dose group was significantly less than that in the controls. Clear evidence of an increased incidence of hepatocellular carcinomas was not found in male mice, but there was evidence of increased tumor incidence in female mice (controls, 1/49; low-dose, 5/46; high-dose, 6/48). Dose-related, statistically significant (p less than 0.05) increases in hepatocellular adenoma incidence occurred in mice of both sexes. TCE was not demonstrated to be carcinogenic in F344/N rats, but it was concluded to be carcinogenic in B6C3F1 mice.

207. **CARCINOGENESIS BIOASSAY OF PENTACHLOROETHANE (CAS NO. 76-01-7) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDY)**
National Toxicology Program
Box 12233, Research Triangle Park, NC 27709
Natl Toxicol Program Tech Rep Ser No. 232; 149 pp. 1983

The carcinogenicity of pentachloroethane (PCE: 99.5% pure) was assayed by administering the chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 75 or 150 mg/kg and to groups of 50 male and 50 female B6C3F1 mice at doses od 250 or 500 mg/kg. Doses were administered to rats for 103 wk and to mice for 41-103 wk. Vehicle controls consisted of groups of 50 rats and 50 mice of each sex. Survival of high-dose rats of each sex was significantly (p less than 0.05) less than that of the controls. Mean body wts of dosed male and female rats were lower than those of control rats during yr 2 of the study. PCE administration resulted in a significant (p less than 0.00 1) and dose-related incidence of chronic, diffuse inflammation of the kidneys in males (control, 4/50; low dose, 14/49; high dose, 33/50). This lesion was distinguishable from nephropathy seen in aging F344/N rats. Mineralization of the renal papilla in dosed males was considered to be secondary to the chronic inflammation, rather than a direct effect of PCE. Rare renal tubular cell adenomas in male rats showed a dose related trend (p less than 0.05), and the incidence in the high-dose group was suggestive (p less than 0.06; 0/50, 1/49, 4/50). Of the high-dose males, 42 died by wk 41 and the 8 survivors were killed at that time. Only 22/50 low-dose male mice survived to the end of the study. All high-dose females died by wk 74, and only 9/50 low-dose females were alive at wk 103. Hepatocellular carcinoma incidence was significantly elevated (p less than 0.001) in all groups of dosed mice, with tumors developing in 4/48 low-dose and 26/44 high dose males and in 1/46 low-dose and 28/42 high-dose females. Early mortality of high dose males precluded evaluation of their lifetime incidence of hepatocellular tumors. There was a significant increase in incidence over that in 25 controls killed at wk 44 (0/25 vs 7/45, p less than 0.05). There also was a significant (p less than 0.001) dose-related increased in hepatocellular adenomas in female mice (2/46, 8/42, 19/45). Initially, PCE was not considered carcinogenic in F344/N rats. However, the National Toxicology Program considered that the tubular cell tumors in male rats indicated a target organ and could have been associated with PCE administration. The chemical was carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes and adenomas in females.

208. **TOXICITY OF 1,2-DIBROMO-3-CHLOROPROPANE (DBCP). I. HISTOPATHOLOGICAL EXAMINATION OF MALE RATS EXPOSED TO DBCP VAPOUR**
Saegusa J, Hasegawa H, Kawai K
Natl. Inst. Industrial Health, 21-1, Nagao 6-chome, Tama-ku, Kawasaki, 213, Japan
Ind Health; 20(4):315-323 1982

Histopathological findings were presented of rats which had inhaled the nematocide 1,2-dibromo-3-chloropropane (DBCP). Eleven rats were continuously exposed to 10 ppm DBCP in air for 14 days, and 5, 2 and 2 rats were killed 1,

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16, and 36 days after exposure, respectively. Of the remaining two rats one died 12 mo after exposure, at which time the other was sacrificed. Marked lesions were induced in the testicles, kidney, and lung. With increasing time after exposure, testicular tubule atrophy became more prominent, resulting in irreversible aspermatogenesis. Proximal tubular necrosis was found in the outer renal medulla. Cytomegaly and necrosis were present in bronchial and bronchiolar epithelial cells. Emphysematous alveolar distention was also observed. The possible induction by DBCP of renal adenocarcinoma and testicular hemangioma in one rat who died at 12 mo is discussed. In a second experiment 19 rats were exposed to 0, 0.3, 1, 3, or 8 ppm of DBCP continuously in air for 14 days. One and 15 days after exposure, one or two rats in each dose group were sacrificed. Pathological changes were found in the 3-and 8-ppm exposure groups. Rats exposed to 3 ppm recovered while those exposed to 8 ppm showed a progressive course. (17 Refs)

209. CARCINOGENICITY AND TOXICITY OF 1,2-DIBROMOETHANE IN THE RAT

Wong LC, Winston JM, Hong CB, Plotnick H
Res. and Development Div., Revlon Health Care Group, 1 Scarsdale Rd., Tuckahoe, NY, 10707
Toxicol Appl Pharmacol; 63(2):155-165 1982

The chronic effects of 1,2-dibromoethane (ethylene dibromide, EDB) were investigated in rats. Three experimental groups were studied: (1) inhalation of 20 ppm EDB over an 18-mo period, (2) 0.05% disulfiram (DS) in the diet for 18 mo, and (3) combined treatment of 20 ppm EDB + 0.05% DS. Rats receiving DS only showed less body wt gain than controls or EDB-exposed rats over the 18-mo period. Rats receiving EDB + DS had lower wt gain than animals receiving either EDB or DS alone. A correlation between low food consumption and low body wt gain was found in rats treated with DS or DS + EDB. EDB-treated or EDB + DS-treated rats exhibited high mortality compared with control rats or those treated with DS alone. While hematological findings were normal for EDB-treated rats, EDB + DB treatment resulted in low hematocrit, hemoglobin, and red blood cell counts. Male rats treated with DS alone did not exhibit any significant histopathological changes except for a higher incidence of hemosiderosis of the spleen; females had a higher incidence of mammary tumors and of hemosiderosis of the spleen. Rats inhaling EDB alone had a higher incidence of tumors, in one or both sexes, in the spleen, adrenal, subcutaneous mesenchymal tissue, and mammary gland compared to controls. Combined treatment with EDB + DS caused an increased incidence of tumors in one or both sexes, in the liver, kidneys, thyroid, lungs, and spleen compared to treatment with either EDB or DS alone. Combined treatment also caused a higher incidence of atrophy of the testes and spleen compared to treatment with EDB alone. These results indicate that DS, a drug used in the treatment of chronic alcoholism, enhances the toxicity and carcinogenicity of EDB. Such an effect may be significant in evaluating the hazards of industrial exposure to EDB in workers who are being treated in alcohol control programs. (37 Refs)

210. MUTAGENICITY, CARCINOGENICITY, AND TERATOGENICITY OF HALOGENATED HYDROCARBON SOLVENTS

Mercier M, Lans M, de Gerlache J
International Program for Chemical Safety, Management Unit, W.H.O., Geneva, Switzerland
Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants. Kirsh-Volders M, ed. New York, Plenum Press, p. 281-324, 1984.

The mutagenicity, carcinogenicity, and teratogenicity of seven halogenated hydrocarbon solvents (dic hloromethane, chloroform, carbon tetrachloride, trichloroethylene, 1,1,1-trichloroethane, 1,2-dichloroethane, and tetrachloroethane) widely used in industry are reviewed. The physical and chemical properties are also presented. Some of these solvents are hepatotoxic or nephrotoxic after acute or long-term exposure. All of these compounds are readily metabolized in vivo, and their degradation products are excreted mainly in urine, with little long-term storage in fat tissues. Chloroform and carbon tetrachloride, as well as dichloromethane, are reported to be teratogenic and/or embryotoxic. Carbon tetrachloride and chloroform are carcinogenic in several species (rats, mice), although negative or only weakly positive in mutagenicity tests. Evidence of carcinogenicity has also been demonstrated for 1,2-dichloroethane. Carbon tetrachloride produces liver tumors in several animal species following different routes of administration. Human cases of hepatomas appearing several years after overexposure to this solvent are reported, as well as an excess of lung, cervical, and skin cancers; a slight excess of leukemia and liver cancers are observed. For trichloroethylene and tetrachloroethylene, however, there is only limited evidence of carcinogenicity and even of mutagenicity. For dichloromethane, although there is no indication of potential carcinogenicity in animal experiments, the information available is not complete enough to draw conclusions; it has been shown to be mutagenic in bacterial test systems, and produced positive results in cell transformation assays. There is sufficient evidence that chloroform and 1,2-dichloroethylene present a carcinogenic risk to humans. Trichloroethylene is the only solvent that presented evidence of teratogenicity. The possible role of organochlorinated solvents in the promoting step of carcinogenesis should also be considered. Such an effect has been already described for carbon tetrachloride. (298 Refs)

211. CARCINOGENICITY OF ORGANIC HALOGENATED COMPOUNDS

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ACS Monogr; (182):525-75 1984

Halogenated hydrocarbons are encountered in numerous occupational and nonoccupational situations; therefore, their carcinogenic potential is a critical concern. Such hydrocarbons are starting materials, intermediates, and by-products for organic syntheses. They are used as fire retardants, solvents, and pesticides and can be found in many commercial products. Although the exact mechanism of chemical carcinogenesis is not clear, two major categories of carcinogens can be distinguished: those acting by genotoxic mechanisms and those acting by epigenetic mechanisms. The differentiation between genotoxic and epigenetic carcinogens requires information on their metabolism; tissue distribution; ro ute and rate of excretion; mutagenicity, especially in the various in vitro systems; interaction with cellular macromolecules, such as proteins or nucleic acids; organ-specificity of cytotoxic effect; and promoting activity. The toxicities and carcinogenicities of specific halogenated compounds are reviewed under

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the following general headings: agents for organic synthesis, fire retardants, miscellaneous agents, polychlorinated biphenyls, and pesticides. The compounds discussed comprise a large and heterogeneous group of chemicals that differ greatly in structure, metabolism, and biological activity; it is, therefore, fitting that they also differ in their modes of carcinogenic action. Some of the compounds clearly are initiators of tumor formation, ie, genotoxic agents, whereas others apparently operate by epigenetic mechanisms, such as recurrent organ-specific cytotoxicity; for some compounds both mechanisms might be operative, while for others data are lacking to make a distinction. The problems of interpreting carcinogenicity data are obviously not specific for the organic halogenated compounds; however, they are particularly pressing for this group of substances. Many of the compounds do not exert their effects by overtly attacking DNA but by some other, poorly specified mechanism. Furthermore, this group contains a large number of chemicals that are widely distributed in the environment and are of great economical value. A particular problem arises from the evaluation of positive results that can only be obtained at very high doses of the test compounds. Although there is a need and a scientific basis for using the maximum tolerable dose in bioassays for carcinogenicity, it has to be realized that a high concentration of these chemicals may exert effects profoundly different from those at low concentrations; still, clarification of the mechanism of chemical carcinogenesis remains the major issue. (469 Refs)

E.

Carcinogenicity Studies Involving Cadmium or Nickel

212. CARCINOGENIC EFFECTS OF CADMIUM ON THE PROSTATE OF THE RAT

Hoffmann L, Putzke HP, Kampehl HJ, Rusbult R, Gase P, Simonn C, Erdmann T, Huckstorf C

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J Cancer Res Clin Oncol; 109(3):193-9 1985

The carcinogenic effects of cadmium were tested in an animal experiment to check the results of epidemiological studies showing that the incidence of prostatic carcinoma is above average in workers industrially exposed to high cadmium levels. For this purpose 1.9 mg CdCl2 (1.2 mg Cd/kg body weight) was injected into the right ventral prostatic lobe of 12-month-old male inbred rats of the Okamoto-toki strain. Simple hyperplasia was found in 38, atypical hyperplasia in 29, atypical hyperplasia with severe dysplasia in 11 and invasive prostatic carcinoma in 5 of 100 animals 270 days after the inj ection. Various mechanisms are discussed in connection with the carcinogenic action of cadmium.

213. CARCINOGENIC PROPERTIES OF NITROSODIMETHYLAMINE WHEN COMBINED WITH BENZENE, CADMIUM, BORON OR ETHANOL

Litvinov NN, Voronin VM, Kazachkov VI

Vopr Onkol; 32(1):80-4 1986

A combination of benzene (5.0 mg/l) or cadmium (0.01 mg/l) with nitrosodimethylamine (drinking water, 9 months) produced a significantly higher tumor incidence in female CBA X C57B1/6 mouse hybrids. The said agents are capable of modifying the carcinogenicity of other substances when present in water in concentrations exceeding the permissible one.

214. THE SYNERGISM OF CADMIUM AND METHYLNITROSAMINES IN MUTAGENESIS AND CARCINOGENESIS (MEETING ABSTRACT)

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Fed Proc; 44(4):925 1985

We have shown (R Mandel and H J-P Ryser, Mutat Res 138:9, 1984) that, while cadmium is weakly mutagenic in S typhimurium, it enhances the mutagenic effect of two methylnitrosamines by 5 to 10 fold. We now show similar effects in cultured mammalian cells as well as a synergism in the development of cancer in rats. Cd is weakly mutagenic in CHO cells yielding up to a 6-fold increase in thioguanine resistant mutants. Cd enhances the mutagenic effect of N-methyl-N-nitrosourea (NMU) in a synergistic manner: at a fixed concentration of Cd, the synergism increases linearly with MNU concentration and at a fixed concentration of MNU, it increases linearly with the cadmium concentration up to 3.7-fold, for induction of resistance to either thioguanine or diphtheria toxin. In male Wistar rats receiving Cd and dimethylnitrosamine in 3 different dose schedules, we find a synergistic increase in the incidence of renal adenoma and adenocarcinoma one yr after exposure. In addition the combined treatment gives rise to tumors in organs that are not usual targets for the single agents. These data show a strong correlation between mutagenesis in bacteria, in mammalian cells, and carcinogenesis in rats. The occurrence at all 3 levels, of synergism between 2 environmental carcinogens, one of which is only weakly active, indicates that weak carcinogens may have strong effects when acting in combination. (1 Ref)

215. SELENIUM PREVENTS THE GROWTH STIMULATORY EFFECTS OF CADMIUM ON BENIGN HUMAN PROSTATIC EPITHELIUM (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 26:122 1985

Association of cadmium (Cd) with a variety of animal tumors has been established. Tumors of the muscle and connective tissue arise at the site of injection. Systemic administration of Cd compounds is associated with interstitial cell tumors of the testis. Increased risk of prostate cancer in men, as a result of occupational and environmental exposure to Cd, has been reported. It is not known wheth er Cd acts as an initiator or a promoter in these situations. Our preliminary studies show that Cd at levels as low as 10(-9) M, stimulates the growth of human prostatic epithelium in vitro. This may be one mechanism by which Cd alters cell behavior. Concentrations higher than 10(-6) M are toxic. Selenium (Se), an essential trace element for mammals, is being investigated for its role in cancer chemoprevention. It reduces the incidence of spontaneous mammary tumors in susceptible strains of mice and inhibits tumor induction in animals by chemical carcinogens. At concentrations between 10(-12) M and 10(-7) M, Se has no stimulatory or inhibitory effects on the growth of benign human prostatic epithelium in vitro. Higher concentrations inhibit growth and it is cytotoxic at 10(-5) M level. The data of particular significance are that when present at 10(-8) M level in culture medium, Se inhibits the growth-stimulatory effects of Cd on prostatic epithelium. These results suggest that Se may be useful in counteracting the effects of cadmium and offer possibilities for investigations on the protective effects of selenium in cadmium-related carcinogenesis.

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216. CARCINOGENICITY OF SINGLE AND MULTIPLE INTRATRACHEAL INSTILLATIONS OF CADMIUM OXIDE IN THE RAT

Sanders CL, Mahaffey JA

Biology and Chemistry Department, Pacific Northwest Laboratory, Richland, Washington.

Environ Res; 33(1):227-33 1984

The carcinogenic effects of single or multiple exposures to intratracheally instilled cadmium oxide, resulting in total doses of 0, 25, 50, and 75 micrograms, were studied in groups of 41 to 48 male Fischer rats. Pulmonary-deposited cadmium oxide did not result in increased numbers of tumors, except in the mammary gland or in rats that had three or more tumor types. Cadmium oxide was not carcinogenic in the lung, liver, kidney, or prostate gland of rats.

217. DOES CADMIUM PLAY A ROLE IN THE ETIOLOGY AND PATHOGENESIS OF PROSTATE CANCER?

Hoffmann L, Putzke HP, Simonn C, Gase P, Russbult R, Kampehl HJ, Serfling D, Erdmann T, Huckstorf C

Z Gesamte Hyg; 31(4):224-7 1985

Keywords (MeSH): Animal; Cadmium/*pharmacodynamics; English Abstract; Male; Prostatic Hypertrophy/chemically induced; Prostatic Neoplasms/*chemically induced; Rats; Rats, Inbred Strains.

218. ASSOCIATION BETWEEN ERYTHROCYTOSIS AND RENAL CANCERS IN RATS FOLLOWING INTRARENAL INJECTION OF NICKEL COMPOUNDS

Sunderman FW Jr, McCully KS, Hopfer SM

Department of Laboratory Medicine, University of Connecticut School of Medicine, Farmington.

Carcinogenesis; 5(11):1511-7 1984

Seventeen nickel compounds were administered to Fischer-344 rats (N = 270) by intrarenal injection (7 mg Ni/rat); the compounds included nickel sulfides, selenides, arsenides, oxide, antimonide, telluride, titanate, ferronickel alloy and metallic nickel dust. Erythrocytosis, as defined by peak hematocrit values that averaged greater than 55% during 1-4 months post-injection, occurred in nine of 17 Ni-treated groups (NiS2, beta NiS, alpha Ni3S2, Ni4FeS4, NiSe, Ni3Se2, NiAsS, NiO, Ni dust). Renal cancers (N = 23) developed within 2 years post-injection in nine of 17 Ni-treated groups (NiS2, beta NiS, alpha Ni3S2, Ni4FeS4, NiSe, Ni3Se2, NiAsS, NiAs, NiFe alloy). The renal cancers included eight fibrosarcomas, five mesangial cell sarcomas, two renal cell carcinomas, two carcinosarcomas, two leiomyosarcomas, two undifferentiated sarcomas, one rhabdomyosarcoma and one nephroblastoma. No erythrocytosis or renal cancers occurred in control rats (N = 97) in three groups treated with the vehicles or metallic iron dust. Rank correlation (p less than 0.0001) was observed between the incidences of erythrocytosis and renal cancers in the 17 Ni-treated groups. Rank correlation (p less than 0.001) was observed between the present incidences of renal cancers and the sarcoma incidences previously reported following intramuscular administration of the 17 nickel compounds to Fischer-344 rats (14 mg Ni/rat). The incidences of renal cancer were not correlated with the mass-fractions of nickel in the 17 compounds, the dissolution half-times of the compounds in rat serum or renal cytosol, or the phagocytic indices of the compounds in rat peritoneal macrophages.

219. TOXICITY AND TRANSFORMATION POTENCY OF NICKEL COMPOUNDS IN BHK CELLS IN VITRO

Hansen K, Stern RM

Danish National Institute of Occupational Health, Hellerup, Denmark.

IARC Sci Publ; 53:193-200 1984

An in vitro bioassay utilizing BHK-21 cells in culture was used to determine the relative transformation potency of nickel metal and a number of nickel compounds. These included as relatively insoluble particulates a known carcinogen, nickel subsulfide (Ni3S2) and several oxides either of commercial interest or found in the working environment in the metal industry [e.g., nickel oxide (NiO)], and a soluble salt, nickel acetate [Ni(CH3COO)2]. Although a wide range of transformation potency was found as a function of the dose of nickel per area of culture, all substances produced the same number of transformed colonies at the same degree of toxicity (e.g., 50% survival). Toxicity may arise from nickel originating in membrane-bound or phagocytized particles, or nickel available from solution. If toxicity is a direct measure of net available nickel, then apparently nickel or nickel ion per se is the ultimate transforming agent, independent of source or uptake mechanism.

220. IN VITRO TOXICITY AND TRANSFORMATION POTENCY OF NICKEL COMPOUNDS

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Danish National Institute of Occupational Health, Hellerup, Denmark.

Environ Health Perspect; 51:223-6 1983

An in vitro bioassay utilizing BHK-21 cells in culture is used to determine the relative transformation potential of a number of nickel compounds including, as relatively insoluble particulates a known carcinogen (Ni3S2) and several oxides either of commercial interest or found in the working environment in the metal industry (e.g., NiO), and a soluble salt [Ni(CH3COO)2]. Although a wide range of transformation potency is found as a function of the dose of Ni per area of culture, all substances produce the same number of transformed colonies at the same degree of toxicity (e.g., 50% survival). If toxicity is a direct measure of intracellular concentration, then apparently nickel per se is the ultimate transforming agent independent of source or uptake mechanism.

F.

Carcinogenicity Studies Involving Other Compounds

221. CARCINOGENICITY OF CHLOROFORM IN DRINKING WATER TO MALE OSBORNE-MENDEL RATS AND FEMALE B6C3F1 MICE

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Fundam Appl Toxicol; 5(4):760-9 1985

The carcinogenic activity of chloroform administered at 0, 200, 400, 900, and 1800 mg/liter in drinking water was studied in male Osborne-Mendel rats and female B6C3F1 mice. A second control group was included in the study and was restricted to the water consumption of the high-dose group. Animals were maintained on study for 104 weeks. Group sizes were adjusted at low doses such that a detectable tumor response would result at the lowest dose if there was a linear relationship with dose, and the higher doses produced responses similar to previous carcinogenesis bioassays of chloroform. The primary finding was that chloroform increased the yield of renal tubular adenomas and adenocarcinomas in male rats in a dose-related manner. For the high-dose group,

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which corresponded to a time-weighted average dose of 160 mg/kg per day for 104 weeks, there was a 14% incidence of renal tubular adenomas and adenocarcinomas, vs 1% in the control group. This compares to a 24% incidence observed when 180 mg/kg per day of chloroform was administered for 78 weeks in earlier studies. In contrast, chloroform in the drinking water of mice failed to increase the incidence of hepatocellular carcinomas in female B6C3F1 mice. The highest dose group received a time-weighted average dose of 263 mg/kg for 104 weeks, resulting in a 5% combined incidence of hepatocellular adenoma and carcinoma relative to a 6% incidence in the control groups.(ABSTRACT TRUNCATED AT 250 WORDS)

222. NEPHROTOXICITY AND RENAL CELL CARCINOMA AFTER USE OF IRON- AND ALUMINUM-NITRILOTRIACETATE COMPLEXES IN RATS

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JNCI; 76(1):107-13 1986

Wistar male rats were tested for nephrotoxicity and carcinogenicity after administration of ferric nitrilotriacetate [(NTA) CAS: 139-13-9] (Fe-NTA) [No. of rats (n) = 24] and Al-NTA (n = 24). The control rats were given AlCl3 (n = 10), NTA (n = 10), and saline (n = 10). Sublethal doses of Fe-NTA [5-7 mg Fe/kg (body wt)] and Al-NTA [1.5-2.0 mg Al/kg (body wt)] were chosen and injected ip for 3 months. AlCl3 and NTA were given in equivalent doses and saline was given in equivalent volumes. All the rats given Fe-NTA or Al-NTA had a depressed weight gain, polyuria, and glucosuria from the 1st week. Histologically, acute tubular necrosis and regenerating epithelial cells were observed. Regenerative atypical epithelial cells in the renal cortex were seen at the termination of Fe-NTA or Al-NTA administration. Control rats had no remarkable changes. After 1 year, primary renal cell carcinoma and metastases to liver, lung, and peritoneum were observed only in Fe-NTA-treated rats (14 of 18 surviving rats). On the contrary, there were no tumors in Al-NTA-treated rats (none of 12 surviving rats). The results suggest that nephrotoxicity and renal cell carcinoma are two independent phenomena from Al-NTA treatment and that a long-term sublethal dose of Al-NTA is not related to renal carcinogenicity.

223. TRISODIUM NITRILOACETATE MONOHYDRATE: PROMOTING EFFECT IN URINARY BLADDER CARCINOGENESIS IN RATS TREATED WITH N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE

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First Department of Pathology, Nara Medical University, Japan.
JNCI; 74(1):235-9 1985

The effect of trisodium nitrilotriacetate monohydrate [(Na3NTA X H2O) CAS: 18662-53-8] on development of urinary bladder tumors in rats initiated with N-butyl-N-(4-hydroxybutyl)nitrosamine [(BBN) CAS: 3817-11-6] was studied. Twenty-one male inbred W rats 6 weeks of age were given drinking water containing 500 ppm of BBN for 4 weeks and then put on diet containing 10,000 ppm of Na3NTA X H2O for 28 weeks. Na3NTA X H2O promoted the development of urinary bladder tumors in rats treated with BBN. The incidences of papilloma and transitional cell carcinomas in the urinary bladder were 90% (18/20) and 25% (4/20), respectively, in rats treated with BBN and then Na3NTA X H2O and 0 in those treated with BBN or Na3NTA X H2O alone. The incidence of papillary or nodular hyperplasia in week 32 was 100% (20/20) in rats treated with BBN and then Na3NTA X H2O and 61% (13/21) in rats treated with BBN only.

224. REVERSIBILITY OF RENAL CORTICAL LESIONS INDUCED IN RATS BY HIGH DOSES OF NITRILOTRIACETATE IN CHRONIC FEEDING STUDIES

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Food Chem Toxicol; 20(6):935-937 1982

The effects in the renal cortex of the male rat of continuous administration of a high dose of nitrilotriacetate (NTA) for 24 mo were compared with those of the administration of a similar dose for 18 mo followed by a 6-mo recovery period on the control diet. The results suggest that discontinuation of treatment interrupts the sequence of events leading to tumor formation. This study indicates that all stages in the proposed pathogenesis of renal tubular tumor formation by NTA, up to the occurrence of adenomatous hyperplasia and neoplasia, are reversible. Apparently, tumor development is dependent on the continuous administration of high doses of NTA in the presence of toxic injury to the majority of nephrons. (Author abstract) (9 Refs)

225. INDUCTION BY PARACETAMOL OF BLADDER AND LIVER TUMOURS IN THE RAT. EFFECTS ON HEPATOCYTE FINE STRUCTURE

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Acta Pathol Microbiol Immunol Scand [A]; 93(6):367-77 1985

Groups of male and female inbred Leeds strain rats were fed diets containing either 0.5% or 1.0% paracetamol by weight for up to 18 months. At the 1.0% dosage level, 20% of rats of both sexes developed neoplastic nodules of the liver, a statistically significant incidence. These rats also showed gross enlargement of their livers and an increase in foci of cellular alteration, the latter also being observed in the low dosage male rats. Papillomas of the transitional epithelium of the bladder developed in all paracetamol-treated groups, and three rats bore bladder carcinomas. However, significant yields of bladder tumours were only obtained from low dosage females and high dosage males. Additionally, 20 to 25% of paracetamol-treated rats developed hyperplasia of the bladder epithelium, which was not coincident with the presence of bladder calculi. A low yield of tumours at various other sites also arose following paracetamol feeding. An electron microscope study of the livers of paracetamol-treated rats revealed ultrastructural changes in the hepatocytes that resemble those that result from exposure to a variety of known hepatocarcinogens.

226. TOXICOLOGY OF MIXED DISTILLATE AND HIGH-ENERGY SYNTHETIC FUELS

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Adv Mod Environ Toxicol; 7:121-32 1984

Turbine engine fuels used in United States Air Force and United States Navy aircraft are mixed distillate hydrocarbons varying in composition from JP-4, which has characteristics similar to gasoline, to JP-8, which is a kerosene-based fuel. Ramjet aircraft fuels, however, consist of synthetic chemicals; JP-10 is the bicyclic compound exo-tetrahydrodi(cyclopentadiene), and RJ-5 consists of hydrogenated dimers of norbornadiene. The toxicologies of the RJ-5, J-10, JP-4, and JP-5 are reported in this chapter; species of animals used included dogs, rats, monkeys, mice, and hamsters. For 90-day continuous experiments, animals were exposed to fuel vapors 24 hr/day, 7 days/wk; for intermittent-exposure (occupational exposure schedule) experiments, ani-

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mals were exposed 6 hr/day, excluding weekends and holidays. Durations of exposure and concentrations of test fuel varied in different experiments. Male rats sacrificed immediately after the 90-day exposures displayed renal proximal tubule degeneration and multifocal dilatation near the corticomedullary junction, caused by plugs of necrotic cell debris. At terminal sacrifice, 19 mo post-exposure, male rat kidneys exhibited marked medullary mineralized casts, multifocal and diffuse hyperplasia of pelvic urothelium, and advanced tubular degeneration compatible with 'old rat nephropathy.' After 1-yr intermittent exposures, extensive proximal tubular degeneration was not observed, but at terminal sacrifice there were significant numbers of renal tumors in male rats. Neither toxic nephropathy nor renal tumors were found in female rats or in other species (mice, hamsters, and dogs) examined. Female mice exposed to hydrocarbon fuels exhibited mild, reversible hepatocellular fatty changes immediately post-exposure; however, these lesions were absent at 24-mo sacrifice. In the several completed studies, the only significant exposure-related responses observed were the dose-dependent toxic nephropathy and renal tumors in male rats and the reversible hepatocellular fatty change in female mice. (14 Refs)

227. PATHOLOGIC FINDINGS IN LABORATORY ANIMALS EXPOSED TO HYDROCARBON FUELS OF MILITARY INTEREST

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Adv Mod Environ Toxicol; 7:133-40 1984

Male and female Fischer 344 rats and female C57/BL6 mice were subjected to subchronic (90-day continuous) and chronic (6 hr/day, 5 days/wk, 1 yr) inhalation exposures to a variety of distillate and synthetic hydrocarbon fuels of military interest. The distillate fuels tested included petroleum- and shale-derived JP-5, petroleum- and shale-derived diesel marine fuel, petroleum-derived JP-4, and decahydronaphthalene (Decalin); the synthetic fuels tested included exo-tetrahydrodi(cyclopentadiene), designated JP-10, and endo-endo-dihydrodi(norbornadiene), designated RJ-5. The experimental design for the 90-day continuous studies included controls and two exposure levels (150 and 750 mg/m3 for the JP-5; 50 and 300 mg/m3 for the diesel marine fuel; 500 and 1,000 mg/m3 for the JP-4; 28.3 and 283 mg/m3 for the Decalin). Each experimental group of animals consisted of 75 male rats, 75 female rats, and 150 female mice. In general, the male rats exposed continuously for 90 days to any of the test fuels developed dose-related nephropathies; such nephropathies were not observed in the female rats, in the exposed mice, or in the controls. The kidney lesions consisted of greatly increased cytoplasmic hyaline droplets in proximal tubular epithelium, necrosis of proximal tubular cells, and intratubular plugs of necrotic cell debris at the junction of the outer and inner stripe of the outer medu lla. Following the 90-day exposure, male rats that were held for lifetime oncogenic evaluation exhibited abundant mineralized casts in medullary tubules, multifocal to diffuse papillary hyperplasia of pelvic urothelium, and accentuated tubular degeneration compatible with progressive nephrosis of old rats. Male rats subjected to the conditions of chronic exposure to the JP-10 at 556 mg/m3 or the RJ-5 at 30 and 150 mg/m3 had significant increases in renal cell tumors, whereas those subjected to the conditions of subchronic exposure to various distillate fuels failed to develop increased kidney neoplasia following lifespan observation. It is proposed that the kidney changes may be related to an inability of renal tubular cells to efficiently digest resorbed alpha 2u globulin, a special protein of male rats, which is synthesized in the liver. (16 Refs)

228. EVALUATION OF THE CANCEROGENIC RISK IN OIL TANKERS DURING REFITTING

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Cancer Detect Prev; 5(3):335-341 1982

Polycyclic aromatic hydrocarbons (PAH) concentration were measured in particles collected in oil tankers during refitting operations in which oxyacetylene flames were used. High levels of benzopyrene (8.3 +-7.2 mg/100 m3) and nitrogen oxides (from 2 to 20 ppm) were detected. The fraction of collected smoke, soluble in cyclohexane, was injected into the peritoneum of Balb/C mice. The frequency of sister chromatid exchange (SCE) induced in bone marrow cells was evaluated. A significant and dose-related increase of SCE was seen, which was comparable to that induced by pure PAH. Based on these results, the presence of other mutagenic substances in addition to benzopyrene was suspected. Chemical and biochemical results confirmed epidemiological evidence of an increased risk of lung and bladder cancer in workers operating inside oil tankers. The authors propose the use of this coordinated approach for an effective primary cancer prevention program in the work place. (Author abstract) (6 Refs)

229. CARCINOGENICITY OF POTASSIUM BROMATE ADMINISTERED ORALLY TO F344 RATS

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JNCI; 71(5):965-72 1983

The carcinogenicity of potassium bromate, a food additive and a neutralizer in permanent waving, was tested by adding it to the drinking water of F344 rats for 110 weeks. Groups of 53 males and 53 females, each, were given solutions of 500 or 250 ppm of potassium bromate or distilled water. A concentration of 500 ppm markedly inhibited an increase of body weight of male rats. The mean survival time was shortest for males given 500 ppm (88.1 +/- 18.1 wk); the survival times of other groups were 1 01-104 weeks. The percentage survival in week 104 was relatively high in all groups, and it was 77.4% for males and 66.0% for females in the control group. High incidences of renal cell tumors (in males and females given 500 or 250 ppm) and mesotheliomas of the peritoneum (in males given 500 ppm) were observed. The incidences of these tumors in test groups were significantly higher than those in controls (P less than.001). It was concluded that, when orally administered under the conditions of this experiment, potassium bromate was carcinogenic to F344 rats.

230. CARCINOGENICITY OF POTASSIUM BROMATE IN F-344 RATS

Obno Y, Onodera H, Takamura N, Imazawa T, Maekawa A, Kurokawa Y

Eisei Shikenjo Hokoku; (100):93-100 1982

Keywords (MeSH): Adenocarcinoma/chemically induced; Administration, Oral; Animal; Bromates/*toxicity; Bromine/*toxicity; English Abstract; Female; Food Additives/*toxicity; Hair Preparations/*toxicity; Kidney Neoplasms/chemically induced; Male; Neoplasms, Experimental/*chemically induced; Rats.

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231. HAIR DYES: LABORATORY EVIDENCE

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Office of Toxicological Sciences, Food and Drug Administration, Washington DC.

IARC Sci Publ; (65):53-6 1985

Keywords (MeSH): Animal; Female; Hair Dyes/*toxicity; Hair Preparations/*toxicity; Male; Mice; Mice, Inbred Strains; Neoplasms, Experimental/*chemically induced; Rats; Rats, Inbred F344.

232. PROMOTION OF 2-(ETHYLNITROSAMINO)ETHANOL-INDUCED RENAL CARCINOGENESIS IN RATS BY NEPHROTOXIC COMPOUNDS: POSITIVE RESPONSES WITH FOLIC ACID, BASIC LEAD ACETATE, AND N-(3,5-DICHLOROPHENYL)SUCCINIMIDE BUT NOT WITH 2,3-DIBROMO-1-PROPANOL PHOSPHATE

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JNCI; 72(2):477-82 1984

The promoting effects of nephrotoxic chemicals, folic acid (FA), N-(3,5-dichlorophenyl)succinimide (NDPS), 2,3-dibromo-1-propanol phosphate (Tris-BP), and basic lead acetate (LAB), on 2-(ethylnitrosamino)ethanol (EHEN)-induced renal carcinogenesis were examined in F344 rats. The rats were treated with 0.1% EHEN in their drinking water for 1 week and then given one of the nephrotoxic chemicals for 35 weeks. FA was injected sc once a week at a dose of 300 mg/kg for the first 8 weeks and thereafter at 100 mg/kg. NDPS, Tris-BP, and LAB were mixed in the diet at concentrations of 0.5, 0.01, and 0.1%, respectively. At week 3 the right kidney was removed to enhance renal neoplasia. Renal cell tumor incidence was significantly increased by both FA and LAB and was slightly increased by NDPS, whereas Tris-BP had no effect. The data show that FA, LAB, and NDPS are promoters of EHEN-induced renal carcinogenesis.

233. BASIC LEAD ACETATE: PROMOTING EFFECT ON THE DEVELOPMENT OF RENAL TUBULAR CELL TUMORS IN RATS TREATED WITH N-ETHYL-N-HYDROXYETHYLNITROSAMINE

Hiasa Y, Ohshima M, Kitahori Y, Fujita T, Yuasa T, Miyashiro A

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JNCI; 70(4):761-5 1983

The development of renal tubular cell tumors by the end of experimental week 32 was studied in inbred Wistar male rats fed a diet containing 1,000 or 500 ppm N-ethyl-N-hydroxyethylnitrosamine (EHEN) for 2 weeks and then given 1,000 ppm basic lead acetate (LA) for 20 weeks. A low dose of LA enhanced the development of renal tubular cell tumors in rats treated with EHEN and increased the number and size of the tumors. The incidence of renal tubular cell tumors at the end of week 32 was 50% in rats treated with 1,000 ppm EHEN for 2 weeks and 100% in rats treated with 1,000 ppm EHEN for 2 weeks and then given 1,000 ppm LA for 20 weeks. The incidences of renal tumors of more than 3 mm in diameter were 70% in rats treated with 1,000 ppm EHEN plus LA and 0% in rats treated with EHEN or LA alone. The low dose of LA showed the enhancing effect of the development of renal tubular cell tumors in rats treated with a subthreshold dose of 500 ppm EHEN.

234. CARCINOGENIC EFFECTS OF LOW DOSES OF CURIUM-244

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No affiliation given

Radiobiologiia; 22(6):845-849 1982

Carcinogenic effects of small doses of Curium-244 (Cm-244) were studied in female random-bred rats subjected to single ip administration of Cm-244 [0.37-37 kilobecquerels/kg (kBc/kg)]. The decrease in the av lifespan was observed only in the rats exposed to the highest Cm-244 dose (481 days, compared with 554 days in controls). Osteosarcomas were observed in 1.3%, 2.1% and 2.6% of the rats exposed to Cm-244 at 0.37, 9.25 and 37 kBc/kg, respectively. Increased incidence of leukemias was observed after exposure to Cm-244 at 9.25 and 18.5 kBc/kg (15.2% and 17%, respectively, compared with 10.7% in control). In addition to osteosarcomas and leukemias, the rats exposed to Cm-244 developed hepatomas, hypernephromas, and lung tumors. (12 Refs)

235. TUMORIGENIC EFFECT OF SODIUM ARSENITE IN RAT KIDNEY

Shirachi DY, Johansen MG, McGowan JP, Tu SH

Department of Physiology and Pharmacology, School of Pharmacy, University of the Pacific, Stockton, California.

Proc West Pharmacol Soc; 26:413-5 1983

Keywords (MeSH): Animal; Arsenic/*toxicity; Body Weight/drug effects; *Carcinogens; Diethylnitrosamine/toxicity; Hepatectomy; Kidney Neoplasms/*chemically induced; Male; Neoplasms, Experimental/chemically induced; Phenobarbital/pharmacodynamics; Rats; Rats, Inbred Strains.

III.

METABOLIC, GENETIC, BIOCHEMICAL, AND MORPHOLOGIC ASPECTS OF URINARY TRACT/PROSTATE CARCINOGENESIS INDUCED BY OCCUPATION-RELATED CHEMICALS

A.

Metabolism of Potential Occupational Carcinogens in Urinary Tract Carcinogenesis

236. PROSTAGLANDIN SYNTHASE-DEPENDENT COOXIDATION AND AROMATIC AMINE CARCINOGENESIS

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Prostaglandins Leukotrienes Cancer; 2:125-69 1985

The subject of prostaglandin synthase (PS)-dependent cooxidation and aromatic carcinogenesis is discussed under the following headings: introduction and overview (aromatic amines and bladder cancer, distribution and characteristics of PS); in vitro studies of PS-dependent metabolism (cooxidation by oxygen insertion; cooxidation by electron withdrawal); in vivo studies implicating PS in bladder cancer; and conclusions and future directions. The following compounds are considered under the section on cooxidation by electron withdrawal: acetaminophen, benzidine, 4-aminobiphenyl, and aminothiazole-substituted 5-nitrofurans. Among the toxic aromatic amines, those that have been reported to be the most reactive in PS-containing incubations also have the lowest oxidation potentials (benzidine and acetaminophen), whereas those that have been reported to be oxygenated in these incubations (2-amino-4-(5-nitro-2-furyl)thiazole and 4-aminobi-

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phenyl) represent amines with higher oxidation potentials, indicating that they release electrons less readily. As a consequence of having provided reducing equivalents via electron withdrawal by the enzyme, the initial amine oxidation products may correspond to the free-radical, semiquinone, or quinoneimine metabolites that have been identified or postulated to be formed. It is unlikely that either the initial enzyme-released product, or the amine-derived entity that actually participates in the carcinogenic reaction (which may not be the same) will ever be identified. A logical experimental approach for confronting this problem may be the study of the stable 'end products' that are ultimately derived from the unstable reactive intermediates, thereby allowing the identities of the latter to be inferred. (111 Refs)

237. CANINE IN VIVO AND IN VITRO METABOLISM OF THE BLADDER CARCINOGEN 4,4'-METHYLENEBIS (2-CHLOROANILINE)

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Michigan State Univ.
Diss Abstr Int kBl, 45(12):3781B 1985

Metabolism of arylamines enhances excretion and results in both detoxified and activated products. Metabolism of known bladder carcinogens has been investigated in the liver, kidney medulla, and bladder but not in the renal cortex. 4,4'-Methylenebis (2-chloroaniline) (MBOCA), an arylamine bladder carcinogen in dogs, is a potential human carcinogen whose biotransformation has not been extensively investigated. The objectives of this investigation were 2-fold: (1) to determine the structure of the major canine urinary metabolite of MBOCA and (2) to test the hypothesis that liver and kidney play a role in arylamine metabolism, using MBOCA as a model. Analysis of the major urinary metabolite of MBOCA demonstrated that it was 5-hydroxy-3,3'-dichloro-4,4'-diaminodiphenylmethane-5-sulfate, an ortho-hydroxy sulfate conjugate. Arylsulfatase but not beta-glucuronidase or citric acid hydrolyzed the metabolite in vitro, indicating that it was a sulfate conjugate. Electron impact mass spectrometry following derivatization and transesterification indicated that the metabolite was ring hydroxylated and fast atom bombardment mass spectrometry confirmed the mol wt was consistent with a sulfate ester. Proton nuclear magnetic resonance studies indicated that the ring substitution was ortho to an amine. The major urinary metabolite of MBOCA corresponded to the same type of conjugate formed in dogs administered similar known bladder carcinogens. Tissue slice incubations from liver and kidney produced glucuronide, glucoside, and sulfate metabolites of MBOCA as determined by enzymatic, physical, and instrumental methods. Liver slices produced seven metabolites separable by high performance liquid chromatography and kidney cortex slices produced six. An N-glycoside and the orthohydroxy sulfate were identified in both organs. A hepatic metabolite was characterized as an o-glucuronide and both liver and kidney produced a metabolite with characteristics of an N-hydroxy-N-glucuronide. 14C-MBOCA bound covalently to both liver and kidney slices in a substrate concentration and time-dependent manner. Binding was not altered in the presence of D(+)galactosamine or p-nitrophenyl sulfate. Binding decreased with a general inhibition of metabolism in the presence of 2,6-dichloro-4-nitrophenol, indicating that oxidation but not conjugation may be important. This investigation provided the first demonstration of production of conjugated arylamine metabolites by the renal cortex. Thus, both liver and kidney may play a role in arylamine metabolism in the dog. (Author abstract)

238. CHEMICAL PROPERTIES OF ULTIMATE CARCINOGENIC METABOLITES OF ARYLAMINES AND ARYLAMIDES

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ACS Symp Ser; (283):341-70 1985

Enzymatic and nonenzymatic activation pathways of arylamines and arylamides to ultimate carcinogens are reviewed, and their relative contributions to the observed carcinogenicity of these compounds are discussed. Arylamides and primary arylamines are initially activated by cytochrome P-450- and flavin-containing monooxygenases to form N-hydroxy arylamides and N-hydroxy arylamines, respectively. These N-hydroxy metabolites are proximate carcinogens; further enzymatic or non-enzymatic processes lead to ultimate carcinogens, defined by their electrophilic reactivity with nucleic acids or proteins. Chemical properties (metabolic formation, reactivity with nucleophiles, solvolysis and redox characteristics, reaction mechanisms, and role as ultimate carcinogenic metabolites) are discussed for the following electrophilic metabolites: N-sulfonyloxy arylamides, N-acetoxy arylamides, N-glucuronyloxy arylamides and arylamines, N-acetoxy arylamines, N-sulfonyloxy arylamines, O-seryl (O-prolyl) est ers of N-hydroxy arylamines, N-hydroxy arylamines (protonation), nitrosoarenes, iminoquinones, diimines, and N-sulfonyloxy and N-arylnitrone derivatives of N-methyl arylamines. (204 Refs)

239. FORMATION AND PERSISTENCE OF ARYLAMINE DNA ADDUCTS IN VIVO

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National Center for Toxicological Research, Jefferson, AR 72079.
Environ Health Perspect; 62:19-30 1985

Aromatic amines are urinary bladder carcinogens in man and induce tumors at a number of sites in experimental animals including the liver, mammary gland, intestine, and bladder. In this review, the particular pathways involved in the metabolic activation of aromatic amines are considered as well as the specific DNA adducts formed in target and nontarget tissue. Particular emphasis is placed on the following compounds: 1-naphthylamine, 2-naphthylamine, 4-aminobiphenyl, 4-acetylaminobiphenyl, 4-acetylamino-4'-fluorobiphenyl, 3,2'-dimethyl-4-aminobiphenyl, 2-acetylaminofluorene, benzidine, N-methyl-4-aminoazobenzene, 4-aminoazobenzene, and 2-acetylaminophenanthrene.

240. THE ROLE OF ARYLAMINE-DNA ADDUCTS IN BENZIDINE CARCINOGENESIS AND MUTAGENESIS (MEETING ABSTRACT)

Kadlubar FF
Natl Ctr. Tox Res., Jefferson, AR
Third International Symposium on Biological Reactive Intermediates. June 6-8, 1985. College Park, MD. abstract 14, 1985.

Benzidine (BZ) is a strong hepatocarcinogen in rodents and induces urinary bladder cancer in dogs and humans. After single or multiple doses of BZ, N-(deoxyguanosin-8-yl)-N'-acetyl-BZ (dG-ABZ) was identified as the major DNA adduct in rat and mouse liver. A comparison of metabolic activation pathways in vitro showed a rapid N-acetylation of BZ to N-acetyl-BZ (ABZ) and a preferential N'-hydroxylation to N'-hydroxy-ABZ. In rats, this N'-hydroxy metabolite is further N'-acetylated to N'-hydroxy-N,N'-diacetyl-BZ which is converted to a reactive electrophile by hepatic N,O-acyltransferase. In mice, however, N'-hydroxy-ABZ appears to be activated to the same reactant by an acetyl CoA-dependent O-acetyltransferase. N'-Hydroxy-ABZ is a strong, direct-acting mutagen in S typhimurium and in CHO cells and forms the same dG-ABZ adduct; and its relative muta-

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genic efficiency (revertants/adduct) exceeds that of all other aromatic amines and hydrocarbons tested. In the dog urinary bladder, BZ is activated by a peroxidative mechanism involving prostaglandin H synthase (PHS) and both a radical and a diimine are formed as intermediates. Synthetic BZ diimine and the PHS-activation of BZ yield the same major DNA adduct, N-(deoxyguanosin-8-yl)-BZ; and reaction stoichiometry and inhibition data indicate that BZ diimine is the major reactant. In human tissues, peroxidative activation of BZ occurs in bladder and colon microsomes; while O-acetyltransferase is active in liver and colon cytosols.

241. METABOLISM AND DNA ADDUCT FORMATION OF 2-ACETYLAMINOFLUORENE BY BLADDER EXPLANTS FROM HUMAN, DOG, MO NKEY, HAMSTER AND RAT

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Carcinogenesis; 5(10):1287-92 1984

Cultured bladder explants from human, dog, monkey, hamster and rat were used to study the metabolism, and DNA-adduct formation of [3H]2-acetylaminofluorene (AAF). After 24 h of incubation with 1 microM [3H]AAF, the organic-soluble and glucuronide fractions represented 29.0-58.4% and 0.7-10.8%, respectively, of the total amount of radioactive material in the medium. In the organic-soluble fraction of all species, the presence of both ring-hydroxylated (at the 7-, 9-, 5-, 3- and 1-carbons) metabolites and N-hydroxy-AAF could be demonstrated, with 7-hydroxy-AAF and 9-hydroxy-AAF being the most ubiquitous metabolic products. In addition, 2-aminofluorene could be detected in all cases with the highest amounts formed by dog bladder explants. Species susceptible to aromatic amine-induced bladder carcinogenesis (human and dog) showed widely varying DNA binding (0.23 +/- 0.20 and 1.95 +/- 1.2 mumol AAF/mol deoxyribonucleotide, respectively), and in explants of the less susceptible species (monkey, hamster and rat) DNA binding was comparable (0.46 +/- 0.21, 0.37 +/- 0.07 and 0.34 +/- 0.27, respectively). Enzymatic hydrolysis of the [3H]AAF - DNA to the nucleoside level revealed that N-(deoxyguanosine-8-yl)-2-aminofluorene, together with small amounts (5.9-15.4% of the total) of its imidazole ring-opened derivative, was the most ubiquitous adduct formed (17.8-47.2% of the total) in all species, except the dog. In dog bladder DNA, N-(deoxyguanosine-8-yl)-2-acetylaminofluorene was the principal DNA adduct (39.0-46.5% of the total) with smaller amounts (15.5-22.2% of the total) in the other species. In addition, small amounts (3.5-8.6% of the total) of another adduct, 3-(deoxygaunosin-N2-yl)-2-acetylaminofluorene, could be detected in all cases. It is concluded that bladder explants of the human, dog, monkey, hamster and rat metabolize AAF mainly to ring-hydroxylated products, but also form small amounts of the proximate carcinogenic metabolite N-hydroxy-AAF. Neither the overall binding of AAF to bladder DNA, nor the formation of specific AAF - DNA adducts is correlated with the relative susceptibilities of these five species to aromatic amine-induced urinary bladder carcinogenesis.

242. MULTIPLE MECHANISMS FOR THE ACTIVATION OF THE CARCINOGEN ACETYLAMINOFLUORENE.

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Icosanoids and Cancer. Thaler-Dao H. Crastes de Paulet A. Paoletti R. eds. New York. Raven Press. p. 49-61. 1984.

A one-electron oxidation activation mechanism for acetylaminofluorene (AAF) is described that could result in formation of deacetylate aminofluorene: DNA adducts. Following in vivo administration of A AF to rats, N-(deoxyguanosine-8-yl)-AAF and (deoxyguanosin-N2-yl)-AAF could be isolated. Peroxidase-H202 catalyzed oxidation also resulted in irreversible binding of 14C-N-OH-AAF to DNA. Substantial inhibition of DNA binding by N-acetyl-methionine and guanosine monophosphate is evidence that the product responsible for DNA binding is N-acetoxy-AAF; adduct formation is the presumed mechanism. In contrast to the free radical-mediated peroxidase-catalyzed activation, this mechanism was much more resistant to reduction by biological hydrogen donors, and denatured DNA was less effective than double-stranded DNA. Rat microsomal-catalyzed binding of 14C-N-OH-AAF to DNA was not affected by NADPH. Binding was inhibited 96% by paraoxon, whereas the peroxidase-H202 catalyzed activation was not affected by paraoxon. Microsomal mixed fraction, however, catalyzed DNA binding by AAF. Polyriboguanylic acid was much more effective than polyriboadenylic acid, and other polyribonucleotides were ineffective, in the peroxidase-H202 catalyzed activation of AAF. DNA binding of N-OH-AAF could be catalyzed by ram vesicular gland microsomes and arachidonate. Microsomal deacetylases may be more important in activation of AAF to DNA reactive species than was realized. (63 Refs)

243. METABOLIC DETERMINANTS IN THE CARCINOGENICITY OF AROMATIC AMINES

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Biochemical Basis of Chemical Carcinogenesis. Griem H. Jung R. Kramer M. Marquardt H. Oesch F. eds. New York. Raven Press. p. 47-56. 1984.

Initial studies on the metabolism of the carcinogen 2-acetylaminofluorene (AAF) revealed that it was mainly metabolized by ring hydroxylation to less toxic, more water-soluble, phenolic compounds. Later, it was found that rats fed AAF excreted a portion of the dose as a conjugate of N-hydroxy-2-acetylaminofluorene (N-OH-AAF); this new metabolite was more carcinogenic than the parent amide, was often active locally, and was active in species such as the guinea pig, which had been shown to be resistant to AAF-induced carcinogenesis. These observations led to the hypothesis that N-hydroxylation was both the first and the obligatory step in the metabolic activation of AAF. However, N-OH-AAF, like AAF had little ability to react under physiologic conditions with proteins or nucleic acids; thus, further metabolic activation appeared to be necessary for conversion of N-OH-AAF to reactive electrophiles. The metabolic activation steps capable of generating both toxic and ultimate carcinogenic forms of the N-OH-AAF were initially thought to be catalyzed by the cytosolic enzymes sulfotransferase and N,O-acyltransferase; however, recent data, obtained in in vitro mutagenesis systems, indicate that the microsomal- and nuclear-associated deacylase (amidase) may play an important role in the me tabolic activation of arylhydroxamic acids. Furthermore, UDP-glucuronosyltransferase and one electron oxidation, ie, radical formation, may also participate in the metabolic activation of such compounds. Based on results of studies using the Salmonella mutagenesis system, it was proposed that, in the context of the multi-stage process involved in chemical hepatocarcinogenesis, sulfotransferase is primarily involved in the promotional aspect of the process by generating the cytotoxic ester of N-OH-AAF and that, in contrast, N,O-acyltransferase and/or deacetylase are responsible for generating the mutagenic species that may initiate the carcinogenic process. (43 Refs)

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244. ORGAN, SPECIES, AND COMPOUND SPECIFICITY IN THE METABOLIC ACTIVATION OF PRIMARY AROMATIC AMINES

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JNCI; 70(6):1077-80 1983

For the evaluation of the role of target tissue activation in the induction of bladder cancer, microsome-mediated N-hydroxylation of the bladder carcinogen 4-biphenylamine (4-BA) was studied in bovine and canine bladder mucosae, relative to the activity in liver. Bovine bladder microsomes mediated the N-hydroxylation of 4-BA at an exceptionally high rate, whereas no detectable activity was found with bovine liver microsomes. Dog bladder microsomes were 40-100 times less active than bovine bladder microsomes and contained approximately one-third the amount of cytochrome P450. Dog liver microsomes were as active as dog bladder microsomes per nanomole P450 and an order of magnitude more active when normalized to microsomal protein. Rat liver microsomes contained the highest level of P450 of all the preparations studied, and N-hydroxylase activity was approximately twice the rate of that of dog liver. The rate of N-hydroxylation of 2-naphthylamine (2-NA) and 1-naphthylamine (1-NA) was compared in bovine bladder mucosa and was found to correlate well with the relative potency of these compounds as bladder carcinogens (4-BA greater than 2-NA greater than 1-NA). Such a comparison could not be made with dog bladder mucosa because of its low N-hydroxylation activity. In addition, bovine bladder mucosa S-9 mutagenic activation of 4-BA, 2-NA, and 1-NA was investigated in Salmonella typhimurium and found to parallel the carcinogenic potency of these compounds. These results demonstrate considerable tissue, species, and compound specificity for the metabolic activation of aromatic amines and provide further evidence in support of bladder activation as a mechanism of aromatic amine-induced bladder cancer.

245. ROLE OF EXTENT AND PERSISTENCE OF DNA MODIFICATIONS IN CHEMICAL CARCINOGENESIS BY AROMATIC AMINES

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Recent Result: Cancer Res; 84:77-89 1983

The initial step in tumor formation with aromatic amines is assumed to involve the modification of nucleic acids. Reactive metabolites bind covalently to purine and pyrimidine bases. The extent of formation of DNA adducts and their persistence is therefore expected to correlate with the biological effect. Using [3H]trans-4-amino-stilbene derivatives as model compounds, several parameters have been measured in susceptible and nonsusceptible rat tissues: total initial DNA binding, initial pattern of adducts, persistence of DNA adducts, accumulation of DNA binding after repeated doses, and persistence of DNA adducts after repeated doses. They did not correlate with tissue susceptibility. The tissue burden decreased in the order: liver greater than kidney greater than lung greater than glandular stomach greater than Zymbal gland. The latter tissue is the primary target for tumor formation. Comparison with other aromatic amines shows that aminostilbene derivatives are no exceptions. The role of specific nucleic acid modifications for mutagenic and carcinogenic effects is also difficult to evaluate in these cases. It is therefore emphasized that modulation of secondary steps in the multistage process may largely influence the final outcome. The role of cell proliferation and its stimulation as well as tumor promoting effects are discussed. Aminostilbene derivatives appear to produce primary lesions quite efficiently in rat liver but lack cytotoxic and promoting properties for this tissue.

246. QUANTITATIVE ASPECTS IN THE METABOLIC ACTIVATION OF AFLATOXIN B1 AND CARCINOGENIC AROMATIC AMINES

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Biochemical Basis of Chemical Carcinogenesis. Griem H, Jung R, Kramer M, Marquardt H, Oesch F, eds. New York, Raven Press, p. 33-45, 1984.

Efforts have been made by investigators to find a quantitative correlation between the extent of DNA modification by chemical carcinogens as the biochemical lesion and the extent of tumor formation as the biological response. It seemed obvious to assume that the availability of reactive metabolites, which is controlled by parameters such as activating and inactivating metabolic pathways and other pharmacokinetic parameters, largely determines the extent of the primary DNA lesions. It was found, however, that these DNA lesions were modulated by the elimination that results from spontaneous hydrolysis of base adducts or from enzymatic repair. Persistent and pertinent DNA damage could, then, be expected to correlate best with biological effect; as brought out in this paper, positive correlations of this kind are difficult to establish, even in detailed in vivo studies of quantitative relationships. Systems that have been studied have involved use of the carcinogens aflatoxin B1, aromatic amines, and trans-4-acetamidostilbene. From the results of such studies, it was concluded that although it remains true that tissue exposure to reactive chemicals or metabolites is a prerequisite for biological effects of chemical carcinogens and that modification of nuclear DNA appears to be a critical biochemical lesion, nevertheless neither initial nor persistent modifications permit assessment of the risk of tumor development in a particular tissue. The data for the aromatic amines indicated that measurement of the extent of metabolic activation does not provide easy access for evaluation of the cytotoxic or promotional potential of these compounds; it even appeared possible that the structural requirements are more specific for promotional effects than for initiation by DNA damage. (42 Refs)

247. ARYLAMINE-DNA ADDUCTS IN VITRO AND IN VIVO: THEIR ROLE IN BACTERIAL MUTAGENESIS AND URINARY BLADDER CARCINOGENESIS

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Environ Health Perspect; 49:125-134 1983

Hepatic N-oxidation, followed by N-glucuronidation, has been proposed as a route of metabolic activation for arylamine bladder carcinogens. It is postulated that the N-glucoronides are transported to the bladder lumen where they are hydrolyzed under slightly acidic conditions to release direct acting carcinogenic and mutagenic N-hydroxyarylamines. In this study, 4-aminobiphenyl (ABP), 1-naphthylamine (1-NA), 2-naphthylamine (2-NA), 2-acetylaminofluorene (AAF), 4-nitrobiphenyl (NBP), benzidine (BZ), and N-acetylbenzidine (ABZ) were administered to male beagle dogs (60 umole/kg), and the bladder epithelium DNA adducts were quantified at various times after treatment. To evaluate the mutagenic potential of these arylamine-DNA adducts, Salmonella typhimurium strains TA 1535 and TA 1538 were incubated with N-hydroxy-2-NA, N-hydroxy-2-aminofluorene, N-hydroxy-ABP, and N-hydroxy-ABZ and the resulting DNA adducts and reversions were quantified. The extent and relative persistence of total DNA binding correlated with the com-

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pounds' ability to induce bladder tumors in dogs. The data suggest that mutagenic N-hydroxyarylamines may be ultimate carcinogens for bladder epithelium. Furthermore, if one assumes that a mutagenic lesion is important for tumor initiation, then C8-deoxyguanosine substitution by these compounds may be significant for urinary bladder carcinogenesis. (43 Refs)

248. SULFATION AND GLUCURONIDATION AS COMPETING PATHWAYS IN THE METABOLISM OF HYDROXAMIC ACIDS: THE ROLE OF N,O-SULFONATION IN CHEMICAL CARCINOGENESIS OF AROMATIC AMINES

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Environ Health Perspect; 49:27-32 1983

Aromatic amines can be metabolized by N-acetylation and N-hydroxylation to hydroxamic acids; these s ubsequently are conjugated to form the N,O-sulfonate and N,O-glucuronide conjugates. The N,O-sulfonates are highly labile metabolites that generate reactive intermediates involved in the covalent binding of the parent compound to protein, RNA and DNA, as well as to low molecular compounds like glutathione. This paper discusses methods used to decrease sulfation in vivo, and thereby to enhance the formation of the more stable N,O-glucuronides from N-hydroxy-2-acetylaminofluorene and N-hydroxy-4-acetylamino-4'-fluorobiphenyl. Acetaminophen pretreatment decreases the sulfate availability, but results in many side effects that complicate the analysis of the results. An 8% casein diet reduces the sulfate availability in the rat to approx 20% of control and thus offers an effective approach to decrease sulfation. The most effective selective inhibition of sulfation is by pentachlorphenol, which very strongly reduces N,O-sulfonation of both hydroxamic acids, and selectively inhibits the formation of DNA adducts that have retained the N-acetyl group. This inhibitor and the related 2,6-dichloro-4-nitrophenol can be employed to study the role of sulfation of hydroxamic acids in initiation and promotion of tumor formation by aromatic amines. (Author abstract) (46 Refs)

249. PROSTAGLANDIN HYDROPEROXIDASE-CATALYZED ACTIVATION OF CERTAIN N-SUBSTITUTED ARYL RENAL AND BLADDER CARCINOGENS

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Environ Health Perspect; 49:33-41 1983

Certain carcinogens are thought to induce renal and bladder cancer following metabolic activation. We propose a model system for this activation and provide supporting experimental evidence. This model proposes that renal and bladder carcinogens' entry into the urinary tract is facilitated, that carcinogens are activated by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase (PES), and that activation results in covalent binding to nucleic acids which can initiate carcinogenesis. Benzidine and the 5-nitrofuran 3-hydroxymethyl-1[(3-(5-nitro-2-furyl)-allydidene)amino]-hydantoin (HMN) were shown to inhibit uptake of organic anions and cations, respectively. Carcinogen binding to DNA was dependent upon specific unsaturated fatty acid substrates and prevented by specific inhibitors of PES, ie, aspirin. Activation with organic peroxides or H_2O_2 was inhibited by antioxidants but not aspirin. Horseradish peroxidase (HRP) metabolized benzidine but not 2-amino-4-(5-nitro-2-furyl)-thiazole (ANFT). Acetaminophen and the 5-nitrofurans ANFT and HMN prevented PES 14C-benzidine metabolism. However, only acetaminophen inhibited HRP metabolism of benzidine. The only aerobic metabolism we have observed of 5-nitrofurans is PES-catalyzed. Aspirin (0.5% in the diet) inh ibited rat bladder hyperplastic lesions induced by feeding 0.1% or 0.2% N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) for 6 or 12 wk. Aspirin reduced bladder prostaglandin synthesis and PES metabolism of FANFT. After 1 yr of an ongoing long-term study, gross examination reveals bladder tumors in 85% of the rats fed 0.2% FANFT and in only 37% of the rats fed FANFT plus 0.5% aspirin. (Author abstract) (31 Refs)

250. A FREE RADICAL MECHANISM FOR ARYLAMINE INDUCED CARCINOGENESIS INVOLVING PEROXIDES

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Biochem Pharmacol; 31(4):607-608 1982

A 1 e oxidation of N-methyl-4-aminoazobenzene (MAB) catalyzes more binding than the 2 e monooxygenase mechanism in the presence of liver sulfotransferase. Covalent binding of (14C)MAB metabolites to exogenous DNA or microsomal protein demonstrated that hydroperoxide was almost 400x more effective than NADPH in catalyzing the binding. NADPH/reductase may reduce the radical formed by the 1 e oxidation pathway of cytochrome P450. The hydroperoxide catalyzed binding was not affected by addition of cytosol, while the NADPH system was markedly enhanced. Addition of ATP and sulfate further enhanced the cytosol effect, suggesting that the cytosol effect was probably due to sulfotransferase acting on the NOH MAB formed by the 2 e oxidation pathway carried out by microsomal amine oxidase/4. No NOH MAB was formed with hydroperoxide. Cytochrome P450 catalyzed both N demethylation and ring hydroxylation of MAB and the N hydroxylation was catalyzed by microsomal amine oxidase. In dogs and mice, the 1 e pathway of the monooxygenase activity of bladder and lung tissue may be responsible for carcinogenesis in these organs following administration of p-dimethylaminoazobenzene. In mouse liver carcinogenesis, both the 1 e and 2 e pathways should be considered. (9 Refs)

251. PHARMACOLOGICALLY ACTIVE METABOLITES OF DRUGS AND OTHER FOREIGN COMPOUNDS: CLINICAL, PHARMACOLOGICAL, THERAPEUTIC AND TOXICOLOGICAL CONSIDERATIONS

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Drugs; 24(6):519-542 1982

Chemically highly reactive metabolites of ingested drugs and other foreign compounds are thought to mediate many different types of serious toxicity including carcinogenesis, mutagenesis, dysmorphogenesis and cellular necrosis. In man, 2-aminonaphthylene, benzidine and 4-aminobiphenyl are known to be bladder carcinogens. Also discussed are metabolites of other compounds including chemotherapeutic agents. Monitoring plasma levels of active metabolites must be considered in therapy. (144 Refs)

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252. A PHARMACOKINETIC MODEL TO PREDICT EXPOSURE OF THE BLADDER EPITHELIUM TO URINARY N-HYDROXYARYLAMINE CARCINOGENS AS A FUNCTION OF URINE PH, VOIDING INTERVAL, AND RESORPTION

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Drug Metab Dispos: 10(6):641-644 1982

Estimation of urinary levels of N-hydroxyarylamines, which are believed to be ultimate carcinogens for the bladder epithelium, has been complicated by the rapid resorption of these metabolites across the bladder wall and by their formation in the urine upon hydrolysis of N-hydroxyarylamine N-glucuronide conjugates. Therefore, a three-compartment pharmacokinetic model was developed with an analog-digital hybrid computer to separate absorption, metabolism, and distribution in the whole animal from events in the bladder lumen (deposition, hydrolysis, and resorption). The total bladder exposure to the carcinogen, N-hydroxy-2-naphthylamine, was then simulated from experimental data; and urine pH and voiding interval, both of which differ widely among species, were tested as variables. For humans and dogs, urine pH was found to be considerably more acidic than monkeys or rats; while voiding intervals in rats were considerably shorter than in monkeys, dogs, or humans. The relative species susceptibilities, indicated by the model as total bladder exposure to the N-hydroxyarylamine metabolite under conditions of normal urine pH and frequency of micturition for each species, were in the order: human greater than or equal to dog greater than monkey greater than rat. This is consistent with the reported carcinogenic potency of 2-naphthylamine in these species and suggests that urine pH and voiding interval are important determinants in aromatic amine-induced bladder cancer. (Author abstract) (17 Refs)

253. BENZIDINE LEVEL IN THE URINE OF RATS SUBJECTED TO ADMINISTRATION OF BENZIDINE DYES

Zhdan VM, Pyler LN
All-Union Cancer Res. Center, Moscow, USSR
Gig Tr Prof Zabol: (1):32-35 1982

To evaluate the mechanism of carcinogenic activity of benzidine (BD), random-bred female rats were subjected to a single, ip or intragastric administration of direct dyes. The urine of exposed animals contained BD. The highest levels of BD were observed after administration of direct blue K and direct diazo-black C. (7 Refs)

254. TOXICOLOGY AND METABOLISM OF NICKEL COMPOUNDS. PROGRESS REPORT, DECEMBER 1, 1983-NOVEMBER 30, 1984

Sunderman FW Jr
Connecticut Univ. Health Center, Farmington. School of Medicine. Available from National Technical Information Service, Springfield, VA as NTIS/DE84014919, 18p 1984

The toxicology of nickel compounds (e.g., NiCl sub 2 , Ni sub 3 S sub 2 , Ni(CO) sub 4) was investigated in rats. The following new knowledge was acquired: (1) renal cytosol from exp 63 NiCl sub 2 -treated rats contains at least ten exp 63 Ni-binding proteins and polypeptides with molecular weights ranging from 168,000 to less than 4,000 daltons; (2) parenteral administration of NiCl sub 2 to rat s transiently diminishes hepatic concentrations of reduced and oxidized glutathione and enhances lipid peroxidation; (3) tetraethylenepentamine is equally effective as diethyldithiocarbamate as an antidote for acute Ni(CO) sub 4 poisoning in rats; (4) Ni(II)-induction of heme oxygenase activity in rat kidney is sustained for only 3 days of repeated treatments and thereafter gradually decreases, indicating adaptive tolerance for Ni(II) toxicity; (5) carcinogenesis bioassays of 17 nickel compounds by ir administration to rats demonstrate close correlation between the induction of erythrocytosis at 1 to 4 months post-injection and the subsequent incidence of renal cancers; (6) immunoreactive erythropoietin concentration is increased in kidney extracts of rats following ir injection of Ni sub 3 S sub 2 , supporting the role of erythropoietin in Ni sub 3 S sub 2 -induced erythrocytosis; (7) arteriosclerotic lesions in Ni sub 3 S sub 2 -treated rats can be visualized by focal fluorescence of hematoporphyrin derivative injected iv 24 hours prior to necropsy; and (8) marked hypernickelemia is a consistent finding in patients with endstage renal disease receiving chronic hemodialysis treatment. (Author abstract) (13 Refs)

255. PHARMACOKINETICS AND METABOLISM OF INDUSTRIAL CHEMICALS

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Prog Drug Metab: 5:311-343 1980

The classical pharmacokinetic methods used in toxicologic evaluation of styrene (rats), 2,4,5-trichlorophenoxyacetic acid (rats and humans), and 1,4-dioxane (rats and humans) were extended to study the interactions of vinylidene chloride (VDC) and tetrachloroethylene (TCE) with tissue DNA. VDC induced kidney tumors and TCE induced hepatocellular carcinomas in male Ha(ICR) mice. VDC (given by inhalation) and TCE (inhalation or po) induced few or no tumors in male Sprague-Dawley rats. Both VDC and TCE caused a dose-related increase in DNA synthesis in their respective target tissues in mice, but not in other mouse tissues or in any rat tissue. In contrast with dimethylnitrosamine, which caused marked DNA alkylation in its target tissue (rat liver), VDC and TCE caused little or no DNA alkylation in their respective mouse target tissues. Mice metabolized inhaled VDC and TCE to a much greater extent than rats. These data supported the concept that VDC and TCE are metabolized in vivo to reactive epoxide intermediates which are responsible for toxicity, including carcinogenic effects. Studies on the mechanism of tumor formation in mice showed that there are at least two distinct mechanisms capable of inducing tumors, which vary in their relative contributions with each chemical. The procedures used for estimating the relative contributions of each mechanism showed that recurrent tissu e injury (an epigenetic mechanism for tumor formation) played a major role in the carcinogenicity of VDC and TCE in mice. The results imply that tumors induced by VDC or TCE should be preceded by detectable levels of tissue damage, and that exposure to VDC or TCE at doses not causing recurrent tissue damage should not result in tumor formation. (46 Refs)

256. MOLECULAR MECHANISMS INVOLVED IN THE TOXICITY OF ORTHOPHENYLPHENOL AND ITS SODIUM SALT

Reitz RH, Fox TR, Quast JF, Hermann EA, Watanabe PG
Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, MI.
Chem Biol Interact: 43(1):99-119 1983

Keywords (MeSH): Alkylation; Animal; Biphenyl Compounds/adverse effects/metabolism/*pharmacodynamics; Bladder Neoplasms/chemically induced; Carcinogens/metabolism/*pharmacodynamics; Chromatography, High Pressure Liquid; Dose-Response Relationship, Drug; DNA/metabolism; Eating; Male; Mutagenicity Tests; Rats; Rats, Inbred F344; Spectrum Analysis, Mass.

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B.
Genetic, Biochemical and Morphologic Aspects

257. N-ACETYLTRANSFERASE PHENOTYPES IN THE URINARY BLADDER CARCINOGENESIS OF A LOW-RISK POPULATION

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Carcinogenesis; 6(2):199-201 1985

N-Acetyltransferase phenotypes were measured in 228 patients with tumours of the urinary bladder and 100 non-cancer controls. 63.6% of the patients and 54.0% of the controls were slow acetylator phenotypes (p less than 0.10). In general, 65% of bladder tumour patients and 59% of controls are slow acetylators (p less than 0.025). N-Acetyltransferases are involved in the metabolism of carcinogenic arylamines and thus could be an important factor in interindividual susceptibility to these agents.

258. N-ACETYLTRANSFERASE PHENOTYPES IN BLADDER TUMOUR PATIENTS WITH AND WITHOUT CARCINOMA IN SITU IN SELECTED SITE BIOPSIES

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Scand J Urol Nephrol; 19(3):203-4 1985

The N-acetyltransferase phenotypes were revealed among 32 patients with bladder tumour and concurrent carcinoma in situ peripherally in the bladder mucosa. Fifty-nine per cent of the bladder tumour patients with concurrent carcinoma in situ were slow acetylator phenotypes in contrast to 68% of 28 bladder tumour patients with normal histological specimens peripherally in the bladder mucosa. This points to a lack of industrial arylamine bladder tumour cases in Denmark.

259. ASSOCIATION OF N-ACETYLTRANSFERASE POLYMORPHISM AND ENVIRONMENTAL FACTORS WITH BLADDER CARCINOGENESIS. STUDY IN A NORTH GERMAN POPULATION

Hansen HP, Agarwal DP, Goedde HW, Bucher H, Huland H, Brachmann W, Ovenbeck R
Institute of Human Genetics, University of Hamburg, FRG.
Eur Urol; 11(4):263-6 1985

The N-acetyltransferase phenotype was determined in 105 German patients with bladder carcinoma and in a control group of 42 healthy subjects. The slow phenotype was significantly more frequent among the patients (61.9% compared to 42.9% in the control group). Potential risk factors like occupational exposure, smoking habits, drug abuse and urological anamnestic predispositions were evaluated in relation to staging and grading of the disease, and acetylator phenotype.

260. HEPATIC ACETYLATOR PHENOTYPE IN BLADDER CANCER PATIENTS

Ladero JM, Kwok CK, Jara C, Fernandez L, Silmi AM, Tapia D, Uson AC
Department of Internal Medicine, Hospital Clinico De San Carlos, Universidad Complutense, Madrid, Spain.
Ann Clin Res; 17(3):96-9 1985

We determined the hepatic acetylator phenotype in 130 patients with transitional-cell carcinoma (urothelioma) of the bladder and, previously in 157 normal control subjects. Eighty-three patients (63.8%) and 90 control subjects (57.4%) were slow acetylators (p greater than 0.05). Patients of both phenotypes did not differ in the consumption of tobacco and coffee. Seventy-five patients were not exposed to occupational risk for bladder cancer and the distribution of acetylator phenotype in them was similar to that of the control group. The other 55 patients had been employed in jobs with an elevated risk for urotheliomas; 41 (74.5%) were slow acetylators, which represented a significant excess over the incidence of slow acetylators in the control group (57.4%) (p less than 0.05); 15 of these patients had worked in jobs with carcinogenic arylamines proven in the workplace environment (11 were slow acetylators). Our results suggest that the slow acetylator phenotype can facilitate the development of urothelioma in individuals with occupational risk.

261. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS

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Dept. Environmental Health, Univ. Washington, Seattle, WA. 98195
J Occup Med; 24(5):369-374 1982

Genetic traits that may predispose individuals to occupational diseases are reviewed. A single-gene difference affecting N-acetyl-transferase (NAT) activity in liver makes individuals slow acetylators (recessive) or rapid acetylators (dominant) of a series of clinically important drugs. NAT is known to be involved in acetylation and thus inactivation arylamines that are potent bladder carcinogens, including beta-naphthylamine, benzidine, 4-amino-biphenyl, and 4-nitrobiphenyl, all of which are used as industrial oxidants. An excess of slow acetylators has been observed in groups with a high incidence of occupational bladder cancers. Genetic control of microsomal oxidizing systems appears to be related to certain occupational disease. Aryl hydrocarbon hydroxylase (AHH) has been shown to be involved in activating many promutagenic and procarcinogenic aryl hydrocarbons, of which benzopyrene is the prototype. The pesticide parathion and its active metabolite paraoxon are inactivated by plasma paraoxonase. Potential genetic predispositions due to differences in tissue sensitivity include the following: hemolysis due to glucose-6-phosphodiesterase; sickle cell trait; plasma alpha-antitrypsin deficiency and pulmonary emphysema; low-back pain, ankylosing spondylitis, and histocompatibility antigen B27; and skin hypersensitivity reactions. Opportunities for research/criteria for development of screening tests are discussed. (35 Refs)

262. GENETICALLY DETERMINED DEBRISOQUINE OXIDATION CAPACITY IN BLADDER CANCER

Carturight RA, Philip PA, Rogers HJ, Glashan RW
Cookridge Hospital, Leeds, UK.
Carcinogenesis; 5(9):1191-2 1984

A report is given of a series of bladder cancer cases examined for the oxidation capacity demonstrated by the use of debrisoquine. No overall association of poor and extensive metaboliser exists between bladder cancer patients and a control group. An absolute association between a benzidine exposed subgroup and metaboliser status exists, but the numbers are too small to indicate the true nature of this relationship.

263. ZINC AND CADMIUM PLASMA AND ERYTHROCYTE LEVELS IN PROSTATIC CARCINOMA, BPH, UROLOGICAL MALIGNANCIES, AND INFLAMMATIONS

Feustel A, Wennrich R
Department of Urology, Markkleeberg Hospital, Leipzig, German Democratic Republic.
Prostate; 8(1):75-9 1986

Zinc and cadmium in both serum and erythrocytes from patients with prostatic carcinoma of different histologies, BPH, other urological tumors, and pyelonephritis were analyzed by atomic absorption spectrometry. The variance of the results

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obtained was very high for each group. No significant differences in the Zn or Cd concentration in either the blood plasma or the erythrocytes could be found between any of the different groups of patients. There were also no trends to be seen in the concentrations of these elements in human blood over a period of months. We conclude that the concentration of Zn and Cd in serum or erythrocytes are not an index for the diagnosis or therapy of prostatic carcinoma, BPH, urological malignancy, or inflammations.

264. ZINC AND CADMIUM CONCENTRATIONS IN WHOLE TISSUE AND IN SEPARATED EPITHELIUM AND STROMA FROM HUMAN BENIGN PROSTATIC HYPERTROPHIC GLANDS

Lahtonen R
Department of Clinical Chemistry, University of Oulu, Finland.
Prostate; 6(2):177-83 1985

Prostate tissues from patients with benign prostatic hypertrophy were separated into epithelial and stromal components and the concentrations of zinc and cadmium were determined in these two fractions and in whole tissue by atomic absorption spectrophotometry. The concentrations of testosterone and 5 alpha-dihydrotestosterone (5 alpha-DHT) were determined by radioimmunoassays. The concentration of zinc was found to be significantly greater (P less than .001) in epithelial than in stromal prepara tions: 17.32 +/- 1.15 vs. 7.29 +/- 0.53 mumol/g dry weight (SEM, n = 15). The concentrations of cadmium in epithelium, 9.55 +/- 1.31 nmol/g dry weight (SEM, n = 15) and in stroma, 6.65 +/- 1.06 nmol/g dry weight (SEM, n = 15), did not differ significantly. The concentrations of zinc and cadmium in whole tissues were 13.88 +/- 1.70 mumol/g dry weight and 8.85 +/- 1.53 nmol/g dry weight, respectively (SEM, n = 15). In epithelial preparations, cadmium and testosterone were inversely correlated, but no other correlations were noted between metal and androgen concentrations in whole tissue, stroma, or epithelium. The results of the present study indicate that zinc preferably resides in the epithelium of human prostatic tissue, particularly in BPH, although the stroma also contains significant amounts of this metal. Cadmium appears to be more evenly distributed between the epithelium and stroma of prostatic tissue and previous findings of high cadmium concentrations in hypertrophic and carcinomatous prostatic tissue were not confirmed.

265. ZINC AND CADMIUM IN CELL FRACTIONS OF PROSTATIC CANCER TISSUES OF DIFFERENT HISTOLOGICAL GRADING IN COMPARISON TO BPH AND NORMAL PROSTATE

Feustel A, Wennrich R
Department of Urology, Markkleeberg Hospital Leipzig, German Democratic Republic.
Urol Res; 12(2):147-50 1984

The concentrations of zinc and cadmium in cellular fractions of normal prostate gland, BPH and prostatic carcinomas of different histological grading were determined by electrothermal atomic absorption spectrometry. We found distinct differences in the content of Zn and Cd in the nuclear fractions of malignant tissues in comparison with BPH and normal prostatic tissues. The highest values of Cd were obtained in the nuclear fractions of poorly-differentiated carcinomas. In these samples we also found a low concentration of zinc. In comparison to this the highest Zn-values were found in the nuclear fraction of the BPH.

266. DETERMINATION OF THE DISTRIBUTION OF ZINC AND CADMIUM IN CELLULAR FRACTIONS OF BPH, NORMAL PROSTATE AND PROSTATIC CANCERS OF DIFFERENT HISTOLOGIES BY ATOMIC AND LASER ABSORPTION SPECTROMETRY IN TISSUE SLICES

Feustel A, Wennrich R
Department of Urology, Markkleeberg Hospital, Leipzig, German Democratic Republic.
Urol Res; 12(5):253-6 1984

The distribution of Zinc (Zn) and Cadmium (Cd) was analyzed in nuclear, mitochondrial and cytosol cellular fractions of prostatic carcinoma of different histological grading, BPH and normal prostate by electrothermal atomic absorption spectrometry (AAS). Distinct differences in Zn and Cd concentration in carcinomatous material in comparison with BPH and normal prostates was found. The highest concentration of Cd and the lowest level of Zn were found in poorly differentiated carcinomas. The results in cellular fractions were compared with investigations on Zn and Cd distribution in prostatic sl ices by laser AAS.

267. ZINC AND CADMIUM CONCENTRATION IN PROSTATIC CARCINOMA OF DIFFERENT HISTOLOGICAL GRADING IN COMPARISON TO NORMAL PROSTATE TISSUE AND ADENOFIBROMYOMATOSIS (BPH)

Feustel A, Wennrich R, Steiniger D, Klauss P
Dept. Urology, 7113 Markkleeberg Hosp., Leipzig, E. Germany
Urol Res; 10(6):301-303 1982

Investigations were made of zinc concentrations in 16 normal prostate glands, 24 adenomas, and 36 carcinomas of different histological grade before hormonal therapy, and of cadmium concentrations in 11 normal prostate glands, 25 adenomas, and 33 carcinomas of varying histological grade. Zn was increased in adenofibromyomatosis, but decreased in prostatic cancer: Zn concentrations (ug/g dried sample) were 348 in normal tissue, 774 in adenoma, 147 in carcinoma, 163 in adenocarcinoma, 109 in solid carcinoma, and 79 in scirrhus carcinoma. In contrast, a continuous increase in Cd concentration was observed in the spectrum of tissue types ranging from normal prostate to adenofibromyomatosis to carcinoma: Cd concentrations (ug/g dried sample) were 0.48 in normal tissue, 1.29 in adenoma, 1.62 in carcinoma, 1.81 in adenocarcinoma, 0.8 in solid carcinoma, and 2.33 in scirrhus carcinoma. A distinct biological antagonistic effect between Zn and Cd in the human prostate may thus be possible, with individual habits determining the accumulation of Cd in a particular patient's tissues. The way in which alterations in Cd and Zn levels influence carcinogenesis remains to be elucidated. (26 Refs)

268. ANTIMONY IN LUNG, LIVER AND KIDNEY TISSUE FROM DECEASED SMELTER WORKERS

Gerhardsson L, Brune D, Nordberg GF, Wester PO
Dept. Environmental Medicine, Umea Univ., S-901 87 Umea, Sweden
Scand J Work Environ Health; 8(3):201-208 1982

Tissue concentrations of antimony in lung, liver, and kidney tissue from a group of deceased smelter workers from northern Sweden have been compared with those of a group of persons without occupational exposure from a nearby area. Neutron activation analysis was used to determine the antimony concentration of lung tissue from exposed workers; these concentrations were 12-fold higher than those of referents (p less than 0.001). For lung tissue there was no tendency towards decreased antimony concentrations with time (up to 29 a) after the cessation of exposure, and this result indicates a long biological half-time. The highest values were

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found for workers who had worked for many yr at the roasters and in the arsenic and selenium departments. There was no significant difference between the antimony concentration of the lung tissue from workers who had died of lung cancer and those of persons who died of other malignancies, cardiovascular disease, or other causes. This finding does not however rule out the possibility of a role for antimony in the etiology of lung cancer among smelter workers since multiple factors may have been operating. The antimony concentration of the liver tissue and the kidney cortex did not differ from the corresponding values of the reference group; this finding indicates either a short biological half-time or insignificance for the systemic distribution of antimony. (Author abstract) (35 Refs)

269. PATHOLOGICAL CHANGES IN THE HUMAN BODY IN ACUTE AND CHRONIC CADMIUM POISONING (59 Refs)

Gazdzik T, Grzybek H, Panz B
Wiad Lek; 37(3):199-203 1984

Keywords (MeSH): Bone Diseases/chemically induced; Cadmium Poisoning/*complications; English Abstract; Food Poisoning/complications; Human; Kidney Diseases/chemically induced; Male; Occupational Diseases/complications; Prostatic Neoplasms/chemically induced; Pulmonary Emphysema/chemically induced; Review.

270. QUALITATIVE ANALYSIS OF COOMASSIE-BLUE-STAINED PROTEINS FROM NORMAL PROSTATE, BENIGN PROSTATIC HYPERTROPHY, OR ADENOCARCINOMA OF THE PROSTATE, SEPARATED BY TWO-DIMENSIONAL PROTEIN ELECTROPHORESIS

Anderson KM, Baranowski J, Bonomi P, Economou SG
Department of Medicine, Rush Medical College, Chicago, IL 60612.
Prostate; 6(3):315-23 1985

Samples from nine normal prostates (N), ten benign hypertrophic prostates (BPH), and eight adenocarcinomas of the prostate (ACP), obtained from the National Prostatic Cancer Project were analyzed by two-dimensional (2D)-protein electrophoresis. Qualitative analysis of Coomassie-blue-stained acidic proteins between pI 3.5 and 6.8 yielded these results: The total number of enumerated proteins was 136 (N), 107 (BPH), and 147 (ACP). Ninety-two denoted proteins were deemed common to the three kinds of samples, three were considered present in N and BPH, 7 in BPH and ACP, and 28 in N and ACP. Thirteen, five, and 20 proteins were detected only in N, BPH, or ACP. These proteins cannot be considered 'unique' to their respective samples, since amounts of protein that do not exceed the minimum sensitivity of the dye may be present in the other samples. The similarity in the patterns of proteins from these three types of prostate samples is consistent with the following hypothesis: The distribution of proteins from histologically ambiguous prostate samples will correlate more closely with these protein profiles than with those associated with cancers originating from other organs.

271. ENZYME HISTOCHEMISTRY IN PLASTIC-EMBEDDED SECTIONS OF NORMAL AND DISEASED KIDNEYS

Alpers CE, Beckstead JH
Department of Pathology, University of California School of Medicine, San Francisco 94143.
Am J Clin Pathol; 83(5):605-12 1985

Interest in the role of mononuclear phagocytes in glomerulonephritis (GN) and in defining markers of renal neoplasms led the authors to study alpha-naphthyl acetate/butyrate esterase (ANAE/ANBE), alkaline phosphatase (AlkP), acid phosphatase (AcP), 5'-nucleotidase (5'N), and ATPase (ATP) activity in paraformaldehyde-fixed, plastic-embedded renal tissue from patients with a variety of pathologic conditions. These conditions included GN, renal tumors, and transplant rejection. Enzymatic staining for ANAE, ANBE, AcP, AlkP, and ATP was generally confined to tubules and collecting ducts in normal kidney. Nine of 10 cases of renal carcinoma had weakly to strongly positive reactions with AlkP, AcP, and ANAE; 9 of 10 cases of Wilms' tumor showed weakly positive reactions with AcP and ANAE, particularly in tubular structures. Severely damaged kidney allografts showed surprising retention of normal histochemical features. In all cases 5'N stained both glomerular capillaries and interstitial vasculature; ATPase and AlkP stained interstitial vessels only. Plastic embedding provides superb preservation of both microscopic anatomy and enzymatic activity, which may allow utilization of enzyme histochemistry for diagnostic and research purposes.

272. BIOCHEMISTRY OF OCCUPATIONAL BLADDER CANCER

Matsushima M, Ando K
Department of Urology, School of Medicine, Tobo University.
Hinyokika Kiyo; 29(11):1383-94 1983

We herein discuss the biochemistry of occupational urinary tract cancer, by reviewing the history of occupational aromatic amine cancer, experimental production of aromatic amine cancers and aromatic amine double cancer. (101 Refs)

273. [URINARY BETA-GLUCURONIDASE ACTIVITY AND ITS DIAGNOSTIC VALUE IN BLADDER CANCER]

Wang X, Chen Y, Bao Z
Bladder Cancer Cooperative Group, PLA General Hosp., Beijing, People's Republic of China
Zhonghua Miniao Waike Zazhi; 3(3):211-213 1982

Results of beta-glucuronidase (GCD) activity determination are presented for 43 patients (36 males, 7 females) with bladder cancer, 72 workers (71 males, 1 female) exposed to benzidines, and 14 normal subjects (9 males, 5 females). Using a urinary GCD value of 300 international phenolphthalein units (IPU) as normal, 67% of bladder cancer patients had GCD values higher than 300 IPU while 36% of normal subjects and 21% of benzidines-exposed workers had higher than normal values. The difference between the urinary GCD activity of bladder cancer patients and normal subjects and those of bladder cancer patients and benzidines-exposed workers was markedly significant. However, there was no significant difference between the urinary GCD values of normal subjects and those of benzidine workers. Among seven cancer patients treated, although most of their urinary GCD values were still over 300 IPU after treatment, these values were significantly lowered. It was concluded that urinary GCD activity does not appear to be suitable for routine use in bladder cancer diagnosis. (4 Refs)

274. INCREASED INCIDENCE OF ANTIBODY IN PRE-MALIGNANT OCCUPATIONAL BLADDER CANCER

Kumar S, Wilson PB, Costello CB
Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
Oncology; 39(2):65-71 1982

Sera from 26.7% of the clinically healthy chemical workers with occupational exposure to bladder carcinogens produced immunofluorescent staining of the intracellular antigens of an allogeneic transitional cell carcinoma of the bladder. The incidence of positives among normal donor's and early stage bladder cancer patients was much lower, viz. 3.6 and 6.7%, respectively. The same sera were also tested for their stain-

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ing reactions against surface antigens of bladder tumor cells. Again sera from a higher proportion of chemical workers (28.6%) was found to produce immunofluorescence compared with normal donors (12.6%) and bladder cancer patients (18.6%). The elevated incidence of antibodies among chemical workers' sera was not due to autoantibodies which were similarly distributed in the three groups. Furthermore, the staining of chemical workers' sera was not tumor type specific as all the sera which stained membrane or intracellular components were found to lose their staining ability on absorption with non-bladder tumor cells. It is proposed that these antibodies result from carcinogenic damage and have a physiological role to play. (Author abstract) (34 Refs)

275. CORRELATION OF UROTHELIAL MORPHOLOGIC CHARACTERISTICS WITH THE DEVELOPMENT OF BLADDER CARCINOMAS IN BALB/C FEMALE MICE ADMINISTERED 2-ACETYLAMINOFLUORENE

Shinohara Y, Frith CH, Greenman DL

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Carcinogenesis; 3(6):615-619 1982

Urinary bladders from 6909 of 24,172 control or 2-acetylaminofluorene (2-AAF) treated female BALB/c mice were examined histopathologically. Dietary doses of 2-AAF ranged from 75 to 150 ppm for up to 33 mo. Urinary bladder epithelial hyperplasia, vacuolization, and inflammation were frequent observations in treated animals and showed a positive correlation with dose level and length of administration of 2-AAF. Concretions were infrequently found and occurred only in controls. Squamous metaplasia, ulceration, and lymphocytic accumulations were infrequently noted but gave some indication of a positive correlation with 2-AAF dose level. Vacuolization was always associated with hyperplasia and/or bladder tumors. Observations on the concurrence of hyperplasia, vacuolization, and neoplasia suggest that both hyperplasia and vacuolization may be precursors of neoplasia. While inflammation was infrequently noted in non-tumor-bearing animals, greater than 90% of the time it was seen in association with tumors and appears to be a response of the bladder to tumor progression. (Author abstract) (20 Refs)

276. SEQUENTIAL MORPHOGENESIS OF URINARY BLADDER TUMORS IN BALB/C MICE GIVEN 2-ACETYLAMINOFLUORENE

Frith CH, Wiley LD, Shinohara Y

(c/o Cross) Div. Management Services, Natl. Center for Toxicological Res., Jefferson, AR, 72079

J Urol; 128(5):1071-1076 1982

The sequential morphogenesis of bladder tumors induced in mice with 2-acetylaminofluorene were studied in order to understand better the morphogenesis of bladder tumors in humans. The study indicated two distinct patterns in the sequential morphogenesis. The first was a focal neovascularization of the transitional epithelium resulting initially in exophytic nodules which appeared more likely to develop into papilloma. The second was a nodular downgrowth of the transitional epithelium resulting initially in endophytic tumors which progressed to endophytic and exophytic carcinomas. Further work is needed to explain the significance of the two separate pathways which sometimes led to the same end result. (Author abstract) (18 Refs)

277. CHROMOSOMES OF PERIPHERAL LYMPHOCYTES OF WORKERS EXPOSED TO BENZIDINE

Qu CY

Chung Hua Chung Liu Tsa Chih; 6(2):86-9 1984

Keywords (MeSH): Adult; Benzidines/*toxicity; Bladder Neoplasms/chemically induced; *Chromosome Aberrations; English Abstract; Female; Human; Lymphocytes/*ultrastructure; Male; Middle Age; Occupational Diseases/chemically induced.

278. EXFOLIATIVE CYTOLOGY FROM THE URINARY TRACT OF WORKERS EXPOSED TO BENZIDINE - A 4-YEAR OBSERVATION

Qi RR

Chung Hua Chung Liu Tsa Chih; 5(3):187-9 1983

Keywords (MeSH): Benzidines/*adverse effects; Bladder Neoplasms/chemically induced/urine; English Abstract; Environmental Exposure; Human; Occupational Diseases/chemically induced/urine; *Occupational Medicine; Urine/*cytology.

IV.

GENERAL REVIEWS AND OTHER RELEVANT STUDIES

279. MUTAGENICITY, CARCINOGENICITY, AND TERATOGENICITY OF INDUSTRIAL POLLUTANTS

Anonymous

No affiliation given

Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants. Kirsh-Volders M, ed. New York, Plenum Press, 336 p., 1984.

Industrial pollutants that present a possible risk to the genetic material of exposed workers are discussed, providing a useful compendium of up-to-date information and references. The cellular factors that modify the expression of mutagenic action into genetic lesions are discussed, and the relation between mutation, repair, and chromosome aberration is explored. The role of chromosomal rearrangement in carcinogenesis is also addressed. The mechanisms whereby a given compound, reaching genetic material, either directly or indirectly, may increase the risk of a cancer developing in the exposed individual and of abnormalities being passed on to his/her progeny are discussed. Comparative tables provide the following data on the compounds studied: chemical properties, production, occurrence, accepted standards in the industry, and positive or negative results with different test systems. The pollutants discussed include heavy metals such as arsenic, beryllium, cadmium, chromium, lead, mercury, nickel, etc; insecticides (chlorinated, organophosphorus, and carbonate insecticides); monomers such as vinyl chloride, acrylonitrile, styrene, vinylidene chloride, butadiene, chlorobutadiene, hexachlorobutadiene, etc; and halogenated hydrocarbon solvents such as chloroform, carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, tetrachloroethylene, dichloromethane, and 1,1,1-trichloroethane. Recent results from mutagenesis and carcinogenesis testing in plant, nonmammalian, and mammalian systems are presented.

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280. MUTAGENICITY, CARCINOGENICITY, AND TERATOGENICITY OF INDUSTRIALLY IMPORTANT MONOMERS

Poncelet F, Duverger-van Bogaert M, Lambotte-Vandepaer M, de Meester C
Laboratory of Toxicology, Tour Ehrlich, 72.37 Av Emm. Mounier, B-1200 Brussels, Belgium
Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants, Kirsh-Volders M, ed. New York, Plenum Press, p. 205-79, 1984.

The toxicity, metabolism, mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity of industrially important monomers such as vinyl chloride (VCM), acrylonitrile (ACN), styrene (STY), vinylidene chloride (VDC), butadiene, chlorobutadiene, and hexachlorobutadiene are discussed. These monomers are extensively used in the production of homo- and copolymeric materials utilized in the manufacture of many and various products, such as food packaging, synthetic textile fibers, synthetic rubber goods, resins, and elastomers. All of them are gaseous or volatile and are generally poorly soluble in water. The exposure of workers in working areas, the atmosphere of which is contaminated by these chemicals, may consequently be a major threat to health. People living in the neighborhood of such establishments are also highly exposed to environmental contamination by the volatile monomers. Exposure to very low but chronic levels is also a risk to human health since toxic, carcinogenic, teratogenic, embryotoxic, and mutagenic effects have been reported. The toxicity is related to their metabolic activation. Metabolism occurs essentially in the liver. Extensive urinary excretion of metabolites might explain the toxic renal effects observed for some of them. VCM induces several types of tumor in experimental animals as well as in exposed workers. VDC, ACN, and STY increase incidence of cancer in experimental animals. All six monomers are able to induce base-pair substitutions in Salmonella typhimurium; VCM, VDC, and ACN produce reverse mutations in Escherichia coli. An increase in gene conversion frequency is noted in Saccharomyces cerevisiae for VCM when tested in vitro in the presence of S9 mix, and for STY when using the host-mediated assay. Chromosome aberrations occur in the cells of animals exposed to VMC and STY vapors. An increased incidence of chromosomal aberrations has been observed among workers exposed to VCM, STY, and chlorobutadiene. Of the six monomers, VCM alone is classified as a human carcinogen; a good correlation exists between its mutagenic properties and its carcinogenicity. Further investigation is needed to evaluate more adequately the toxicogenetic potential of the other five monomers. (399 Refs)

281. CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY OF INDUSTRIALLY USED METALS

Leonard A, Gerber GB, Jacquet P, Lauwerys RR
Dept. of Radiobiology, CEN-SCK, B-2400 Mol, Belgium
Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants, Kirsh-Volders M, ed. New York, Plenum Press, p. 59-126, 1984.

The mutagenicity, carcinogenicity, and teratogenicity of industrially used metals such as arsenic, beryllium, cadmium, chromium, lead, mercury, nickel, and other metals are discussed. Other topics discussed include risks and their assessment, metabolism and toxicity, mechanisms of metal toxicity, mutagenesis tests and their interpretation, mechanisms and evaluation of carcinogenesis, and action on the developing organisms. The metallurgical industry contributes most to the dispersion of metals in the environment, and this has become a matter of increasing concern, since several metals have been shown to have mutagenic, carcinogenic, or teratogenic potential. For certain of these metals, such as beryllium and cobalt, the risk of excessive exposure is usually restricted to persons occupationally exposed or living near sources of emission, whereas for other metals, such as arsenic, lead, cadmium, and mercury, such exposure can extend to large parts of the general population. The metals can be classified according to their mutagenic potential (from most to least) as follows: Cr, Be, As, Ni, Hg, Cd, Pb. Taking into account the number of persons potentially exposed, metals can be classified according to their carcinogenic risks (from most to least) as follows: As, Cr, Ni, Be, Pb=Cd=Hg, the latter three metals being practically noncarcinogenic in man. Information on the teratogenic risks is derived almost exclusively from experiments on animals, mainly rodents; no epidemiological data are available, as was the case with carcinogenesis and mutagenesis. Moreover, the conditions of such experimental exposure (injection of high doses) usually differ greatly from those under which man may be exposed, so that extrapolation to man is difficult. The risk of malformation seems greatest for cadmium followed by arsenic, nickel, and chromium. The greatest risk to human development originates from the toxicity of mercury and lead in the developing central nervous system. (556 Refs)

282. GENETIC TOXICOLOGY OF 14 AGENTS CAUSALLY ASSOCIATED WITH CANCER IN HUMANS

Waters MD, Garrett NE, Covone-de Serres CM, Howard BE, Stack HF
Genetic Toxicology Div., Health Effects Res. Lab., U.S. Environmental Protection Agency, Res. Triangle Park, NC 27711
Environ Sci Res; 31:625-87 1984

Currently available qualitative and quantitative information obtained from genetic bioassay systems for 14 agents or groups of putative human carcinogens is summarized and evaluated. The compounds were (1) human respiratory tract carcinogens (bis(chloromethyl)ether and chloromethyl methyl ether, mustard gas, arsenic compounds, chromium compounds, and asbestiform materials), (2) hematolymphopoietic system carcinogens (benzene, melphalan), (3) bladder carcinogens (4-aminobiphenyl, benzidine, 2-naphthylamine, chlornaphazine, and cyclophosphamide) and (4) two agents, diethylstilbestrol and vinyl chloride, that could not be assigned to one of the three target systems. Test responses were obtained for approx 100 test systems, and included organisms from prokaryotes through mammals. Genetic endpoints of the test systems included point mutation, primary DNA damage, chromosomal effects, cellular transformation, and sperm morphology (mammals). Quantitative responses for each compound in each test system were graphed by computer, and the genetic spectra were evaluated by application of simple pattern recognition techniques and statistical methods. Most of the data for the 14 agents were developed in relatively few screening tests, and most of those involved microorganisms. As the amount of bioassay data has increased it has become possible to test the hypothesis that similar chemical compounds, or those possessing specific reactive groups, will exhibit similar spectra of genetic activity. (257 Refs)

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283. IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISK OF CHEMICALS TO HUMANS. CHEMICALS, INDUSTRIAL PROCESSES AND INDUSTRIES ASSOCIATED WITH CANCER IN HUMANS. IARC MONOGRAPHS, VOLUMES 1 TO 29

International Agency for Research on Cancer
Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; (Suppl 4): 292 pp., 1982

Chemicals, groups of chemicals, industrial processes, and occupational exposures for which some data on carcinogenicity in humans were available were reevaluated, both on the basis of studies summarized previously in the monographs and of data published subsequently. Similar data from studies on experimental animals and from short-term tests are also summarized. Topics considered included short-term tests used for the detection of potential chemical carcinogens, uses of short-term tests, assessment of evidence for carcinogenicity from studies in humans and in experimental animals, assessment of data from short-term tests, and evaluation of carcinogenic risk to humans. Descriptive summaries of the data on the basis of which the chemicals, industrial processes, and industries were evaluated for carcinogenicity in humans are presented. Seven industrial processes and occupational exposures and 23 chemicals and groups of chemicals were causally associated with cancer in humans; 61 chemicals, groups of chemicals, or industrial processes were considered probably carcinogenic in humans; and 64 chemicals, groups of chemicals, industrial processes and occupational exposures could not be clas sified. (1207 Refs)

284. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME AROMATIC AMINES, ANTHRAQUINONES AND NITROSO COMPOUNDS, AND INORGANIC FLUORIDES USED IN DRINKING-WATER AND DENTAL PREPARATIONS

IARC Working Group
International Agency for Research on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 27:1-7 1982

Monographs on carcinogenicity data for groups of chemicals to which humans are known to be exposed are presented, and some aromatic amines and anthraquinones (used mainly as dyestuff intermediates), two nitroso compounds, and inorganic fluorides used in the fluoridation of drinking water or in dental preparations are included. The importance of data on the purity of chemicals used in animal carcinogenicity experiments and in mutagenicity tests was emphasized. Aromatic amines discussed include aniline and aniline hydrochloride, ortho-anisidine and para-anisidine and their hydrochlorides, 4-chloro-ortho-phenylenediamine and 4-chloro-meta-phenylenediamine, meta-cresidine and para-cresidine, 2,4-diaminoanisole and 2,4-diaminoanisole sulfate, 4,4'-methylenebis(N,N-dimethyl)benzenamine, 1,5-naphthalenediamine, 2,2',5,5'-tetrachlorobenzidine, 4,4'-thiodianiline, ortho-toluidine and ortho-toluidine hydrochloride, and 2,4,5-trimethylaniline and 2,4,6-trimethylaniline and their hydrochlorides. Anthraquinones include 2-aminoanthraquinone, 1-amino-2-methylanthraquinone, and 2-methyl-1-nitroanthraquinone. Nitroso compounds include N-nitrosodiphenylamine and para-nitrosodiphenylamine. An appendix on the epidemiological evidence relating to the possible carcinogenic effects of hair dyes in hairdressers and users of hair dyes is included. Critical analyses of the data presented are made in order to assist national and international authorities in formulating decisions concerning preventive measures. (744 Refs)

285. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY

IARC Working Group
Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum. Vol. 28, 486 pp., 1982.

The carcinogenic risks of exposures to workers in the rubber industry is evaluated. Manufacturing of tires, and other rubber goods are considered with respect to exposures incident to the mixing of elastomers with chemicals and their subsequent conversion into finished products. An historical overview is presented with discussion of the origins of the rubber industry and the developing rubber industry and its occupational health hazards. Manufacturing processes are described for tires, tubes, remolds, and retreads; general rubber goods such as wire and cables, belting, hose, ebonite, rubber footwear, food processing equipment, aircraft deicing equipment, automobile parts; proofed rubber fabr ics, adhesives and sealants; and dipped latex products and forms. The chemistry of rubber compounding is reviewed. Exposures in the workplace are discussed with respect to controls, protective equipment, work practices; studies of exposures in the workplace; and biological monitoring. Biological effects include carcinogenic, mutagenic, and teratogenic effects of exposure to accelerators, antioxidants, curing agents; solvents; monomers; talc; carbon blacks; aromatic amines; mineral oils, tar products and polycyclic aromatic hydrocarbons; nitroso compounds; phthalate and adipate esters; and curing fumes and other emissions. Effects in humans other than cancer including dermatologic respiratory, and reproductive, are discussed. Epidemiological studies of carcinogenicity in humans are reviewed: definite associations with cancer of the urinary bladder, lymphatics, stomach, lung, and perhaps, other sites, have been made. (367 Refs)

286. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: WOOD, LEATHER AND SOME ASSOCIATED INDUSTRIES

International Agency for Research on Cancer
Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum. Vol. 25, 412 pp., 1981.

The carcinogenicities of chemicals related to the wood, leather, and associated industries are summarized. The industries are described in such a way as to indicate exposures to all known exogenous and endogenous chemicals involved in the processing or use of a material. All available epidemiological data in specific occupations within the selected industries are reviewed. The evaluations made in the present monographs rely almost entirely on epidemiological data, which take into account the effects of the entire spectrum of human exposures in a given situation. One of the aims of the present monographs is to identify the possible contributing roles of individual chemicals in the carcinogenic effect of a known or suspected exposure to a complex mixture. General remarks on wood, leather, and some associated industries are presented. Separate monographs are presented on wood (lumber and sawmill, furniture and cabinet-making, carpentry and joinery, and the pulp and paper industries) and leather tanning and processing, boot and shoe manufacture and repair, and leather goods manufacturing industries. (416 Refs)

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287. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS. SOME METALS AND METALLIC COMPOUNDS

International Agency for Research on Cancer (IARC)
World Health Organization (WHO), Geneva, Switzerland
IARC Monogr Eval Carcinog Risk Chem Hum. Vol. 23, 438 pp., 1980.

This is an introduction to critical reviews on the human carcinogenic risk of the elements and compounds of arsenic, beryllium, chromium, and lead. The information derives from a consensus meeting held under WHO-IARC auspices at Lyon in October 1979. The introduction includes these topics: background for these studies, objective and scope; selection criteria for chemicals in the monographs; study procedures and information sources; data available for evaluations; tasks of the Working Group; principles for evaluating the carcinogenic risk of chemicals (experimental evidence, its qualitative and quantitative aspects, and statistical analyses of animal studies; evidence of carcinogenicity in humans; and experimental data relevant to the evaluation of carcinogenic risk to humans); explanatory notes on the monograph contents (chemical and physical data; substance production, use, occurrence, and analysis; biological data relevant to the evaluation of carcinogenic risk to humans; modes of evaluation and summary of data); regulatory status; problems in evaluating carcinogenic risk of metals and their compounds; and short term testing. (no Refs)

288. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS. POLYNUCLEAR AROMATIC COMPOUNDS, PART 4, BITUMENS, COAL-TARS AND DERIVED PRODUCTS, SHALE-OILS AND SOOTS

Anonymous
IARC Monogr Eval Carcinog Risk Chem Hum; 35:1-247 1985

Keywords (MeSH): Air Pollutants, Environmental/*toxicity; Animal; Carbon/*toxicity; *Carcinogens; Coal Tar/*toxicity; Human; Hydrocarbons/*toxicity; Polycyclic Hydrocarbons/*toxicity; Silica/*toxicity.

289. TARGET ORGANS FOR CARCINOGENICITY OF CHEMICALS AND INDUSTRIAL EXPOSURES IN HUMANS: A REVIEW OF RESULTS IN THE IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Merletti F, Heseltine E, Saracci R, Simonato L, Vainio H, Wilbourn J
Epidemiologia dei Tumori, Universita di Torino, Italy
Cancer Res; 44(5):2244-50 1984

Epidemiological observations indicate that cancers affecting different organs and systems in humans have different causes. At the descriptive level, cancer incidence and mortality rates exhibit patterns of geographic and temporal variation which are distinct and separate for each cancer site and even, at a given site, for different histological types (for instance, increasing squamous cell carcinoma of the lung and decreasing stomach cancer in most developed countries in recent decades). The existence of these distinct patterns in itself indicates that different causes are at the origin of cancers at different sites. Hence, it is of scientific and practical importance not only to identify agents that are carcinogenic to humans but also to specify as definitely as possible the target organ(s) of their action. This is done in the present review of results in the International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.

290. DATA ON THE CARCINOGENICITY OF CHEMICALS IN THE IARC MONOGRAPHS PROGRAMME

Vainio H, Hemminki K, Wilbourn J
International Agency for Research on Cancer, Lyon, France
Carcinogenesis; 6(11):1653-65 1985

Data were extracted from IARC Monographs volumes 1-38 on chemicals and exposures for which some data on carcinogenicity in humans, or sufficient evidence of carcinogenicity in experimental animals existed. In all, 288 chemicals, industrial processes and complex mixtures fulfilled these criteria. For 30 chemicals or mixtures of chemicals, and nine industrial processes, there was sufficient evidence of carcinogenicity in humans; and for 63 chemicals and mixtures of chemicals and for five industrial processes, there was evidence that these exposures were probably carcinogenic to humans. For 61 chemicals or groups of chemicals and six industrial processes or occupations, no evaluation of carcinogenicity to humans could be made. For 115 chemicals there is sufficient evidence of carcinogenicity to experimental animals, but no epidemiological data are available. Publications not earlier referred to on the carcinogenicity of these chemicals and exposures were found for approximately 70. A call is made for further information on these exposures with a view to updating the IARC Monographs.

291. HANDBOOK OF TOXIC AND HAZARDOUS CHEMICALS AND CARCINOGENS

Sittig M
Princeton University
Handbook of Toxic and Hazardous Chemicals and Carcinogens. Sittig M, Park Ridge, New Jersey, Noyes Publications, 950 p., 1985.

Concise chemical, health, and safety information on nearly 800 toxic and hazardous chemicals is presented. Included are the Environmental Protection Agency (EPA) Priority Toxic Pollutants; all of the substances whose allowable concentrations in workplace air were adopted or proposed by the American Conference of Government Industrial Hygienists; those substances considered to date in the Standards Completion Program of the National Institute for Occupational Safety and Health (NIOSH); most of the chemicals classified as EPA 'hazardous wastes' and 'hazardous substances'; a majority of the chemicals reviewed in EPA 'CHIPS' documents; and most of the chemicals reviewed in NIOSH Information Profiles. Additional sources include the US National Toxicology Program, the Dutch Association of Safety Experts, the Dutch Chemical Industry Association, the Dutch Safety Institute, the International Labour Organization's Encyclopedia of Occupational Health and Safety, the United Nations' International Register of Potentially Toxic Chemicals Legal File, and the journal 'Dangerous Properties of Industrial Material Reports.' The chemicals are presented alphabetically and each is classified as a 'carcinogen,' 'hazardous substance,' 'hazardous waste,' and/or a 'priority toxic pollutant,' as defined by federal agencies, and explained in the volume's introduction. Particular attention is given to delineation of the identity and properties of those chemicals now known to be carcinogens.

292. CANCER CAUSING CHEMICALS

Sax NI, Weisburger EK, Schottenfeld D, Haas J, Feiner B, Castelman BI, Lewis RJ
No affiliation given
Cancer Causing Chemicals. New York, Van Nostrand Reinhold Company, 466 pp., 1981.

Chemical carcinogenesis and its relevance for the general population, carcinogens in the workplace, control of workplace carcinogens, and regulations affecting use of carcino-

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gens are discussed. Approx 25,000 synonyms and cross references to each of the 2,400 basic carcinogens (BC) are listed, described and discussed. Carcinogenicity of each of the BC is rated as 'conclusive', 'suggestive', or 'indeterminate' based upon literature research against criteria applied to this data by means of computer. Smoking, radiation, location or geographic location, drug use, congenital and genetic diseases, congenital defects, familial susceptibility, other diseases increasing the risk of developing neoplastic diseases, precancerous conditions, acquired diseases, and life-style are responsible for much of the general cancer incidence. Principles of non-human testing for chemical carcinogenicity are discussed with respect to the relevance of animal and in vitro studies for predicting human risks. Current concepts of prevention and control of occupational cancers are presented. Process, plant, and equipment design; exhaust ventilation; respiratory protection; protective clothing and personal hygiene; monitoring; and specific control techniques are included in the control of workplace carcinogens. Products and wastes containing carcinogens should be appropriately packed, labeled, and disposed of. The use of recognized carcinogens should be fully justified in terms of their need in society and available alternatives. (312 Refs)

293. CHEMICAL CARCINOGENS AS LABORATORY HAZARDS

Searle CE
Univ. of Birmingham, Dept. of Cancer Studies, The Medical School, Birmingham B15 2TJ, England
ACS Monogr; (182):303-23 1984

The continually increasing attention paid in recent years to environmental aspects of chemical carcinogens has tended to focus on chemicals encountered as environmental pollutants in industry or as additives and contaminants in the diet. Carcinogenic hazards may also be encountered, however, in smaller-scale laboratory work. Because laboratory work involves the use of chemicals on a scale that is generally small compared with that of the manufacturing industry, it seems reasonable to expect that any carcinogenic hazards are correspondingly less; this assumption cannot be taken for granted, however, since one can envisage the possibility of workers in a poorly run laboratory being in fact at greater risk than those in a factory maintaining a high standard of industrial hygiene. At present there is relatively little epidemiological evidence on which to base conclusions about actual carcinogenic hazards in the laboratory. Laboratory uses of carcinogens have not been confined to clinical chemistry; moreover, the range of known carcinogens of various chemical classes is continually expanding. Therefore, suspicions that some chemists might develop cancer as a result of their work are warranted, and several epidemiological studies have now been carried out to investigate this possibility. With respect to this possibility, the following topics are discussed: epidemiological studies of chemists, studies of some other chemically exposed populations, other analytical uses of carcinogenic amines, possible carcinogenicity of some other reagents, potency and volatility of chemical carcinogens, laboratory precautions with carcinogens, and carcinogens in science education. The range of known carcinogens is now so great that their complete elimination from the environment is clearly impracticable. Nevertheless, in many situations, substitution of carcinogens by safer materials is possible. Where carcinogens of significant risk still have to be used, it must be with full knowledge and observance of safety precautions now regarded as essential to protect both the operator and other people. (90 Refs)

294. PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY. VOLUME 2A. TOXICOLOGY

Clayton GD, Clayton FE
San Luis Rey, CA
Patty's Industrial Hygiene and Toxicology. Volume 2A. Toxicology. New York, John Wiley and Sons, 1467-2878 pp., 1981.

Toxicity and other data are presented for elements and compounds that are currently of primary interest to industry. Individual chapters describe the sources and production, uses and industrial exposures, physical and chemical properties, acute and chronic toxicity, carcinogenicity, and mutagenicity of 40 metals, organic sulfur compounds, epoxy compounds, esters, ethers, aromatic nitro and amino compounds, phenols and phenolic compounds, aldehydes and acetals, heterocyclic and miscellaneous nitrogen compounds, and phosphorus, selenium, and tellurium. Analytic procedures and recommended threshold limit values also are discussed. (4197 Refs)

295. URINARY BLADDER CARCINOGENESIS

Cohen SM, Greenfield RE, Friedell GH
Dept. Pathology, Univ. Nebraska Medical Center, Omaha, NE, 68105
Pathobiol Annu; 12:267-280 1982

Various aspects of urinary bladder carcinogenesis are reviewed. Morphologic stages in experimental bladder carcinogenesis may involve alterations of the urothelium and epithelium. Examples of bladder carcinogenesis as a multistage process are presented. Also considered are the roles of urine, tryptophan metabolites, human bladder carcinogens, and N-nitroso compounds (which may be involved in induction of bladder cancer in people infected with Schistosoma hematobium). (94 Refs)

296. BIOMONITORING OF EXPOSURE TO POTENTIAL MUTAGENS AND CARCINOGENS IN INDUSTRIAL POPULATIONS

van Sittert NJ, de Jong G
Health, Safety and Environment Division, Shell Internationale Petroleum Maatschappij BV, The Hague, The Netherlands.
Food Chem Toxicol; 23(1):23-31 1985

Methods for monitoring exposure to potential industrial mutagens and carcinogens fall into two distinct groups. The tests in the first group measure the concentration of the substance, of its metabolites or of the products of its reaction with cellular macromolecules, in biological media. Such tests include the determination of urinary metabolites of the chemical, the measurement of nucleic-acid or protein adducts and the determination of urinary thioethers. The second group comprises assays of biological endpoints that may be the result of the organism's reaction to exposure. These endpoints include chromosomal aberrations in peripheral lymphocytes and sister chromatid exchanges. Each test has advantages and limitations that will affect its suitability for use in specific industrial situations.

297. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H
Lab. Government Chemist, London, England
IARC Sci Publ Issue 40, 347 pp., 1981.

Analysis of industrial and non-industrial aromatic amines (AA) and azo dyes (AD) is reviewed. AA and AD are considered with respect to biological activity (carcinogencity of AA and AD and their role in the development of human cancer, metabolic activation of AD), occurrence and monitoring in industry (biological monitoring of AA and their

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metabolites using short-term tests for carcinogenicity, AA of major industrial importance, survey of technics for estimating and monitoring AA of major industrial importance), AA and dyes in non-industrial exposures (mutagenic heterocyclic amines in cooked food; survey of the analysis of 2-acetylaminofluorene; overview of the toxicity, metabolism, and analysis of phenacetin; food colors), methods of analysis for AA and dyes in foods (analysis of 2-acetylaminofluorene in animal feed by spectrophotofluorescence, identification of water-soluble colors in food using paper and thin-layer chromatography, extraction of water-soluble colors from food using polyamide columns). (667 Refs)

298. OCCUPATIONAL AND COMMUNITY EXPOSURES TO TOXIC METALS: LEAD, CADMIUM, MERCURY AND ARSENIC

Landrigan PJ
Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. for Occupational Safety and Health, 4676 Columbia Parkway, Cincinati, OH, 45226
West J Med; 137(6):531-539 1982

Sources of exposure, toxicity, evaluation, and diagnosis of exposure to toxic metals (lead, cadmium, mercury, and arsenic) are presented. The extent of the problem of toxic metal exposure among residents of the United States is illustrated by recently developed data from the National Health and Nutrition Evaluation Survey. Lead is a carcinogen in three animal species, cadmium causes cancer of the prostate and possibly of the lung, and arsenic causes skin cancer. (81 Refs)

299. CADMIUM

Lauwerys RR
Department of Occupational Medicine and Hygiene, University of Louvain, 30.54 Clos Chapelleaux-Champs, 1200 Brussels, Belgium
Biological Monitoring and Surveillance of Workers Exposed to Chemicals. Aitio A, Riihimaki V, Vainio H, eds. Washington, Hemisphere Publishing Corporation, p. 41-7, 1984.

Monitoring of Cd exposure, and the relationship between occupational exposure levels and kidney dysfunction are reviewed. All available human and animal data indicate that (1) before all body binding sites for Cd become saturated, urine Cd concentration can be used as an indirect indicator of body burden; (2) when exposure is very intense Cd in urine may be influenced by current exposure; (3) renal disturbance is usually associated with increased Cd excretion in urine; and (4) a high urine Cd concentration may not necessarily indicate renal disturbance. In occupationally exposed persons, blood Cd level is a good indicator of exposure during recent months prior to sampling. Following exposure to Cd, kidney Cd level increases progressively up to a critical level, and then kidney dysfunction ensues, with a progressive loss of Cd from the kidney. To prevent renal dysfunction in adult male workers exposed to Cd, the amount of Cd stored in the kidney should be below 200-250 ppm, levels which correspond to a urinary excretion of 10-15 microgram Cd/g creatine. For blood, a level 1 microgram Cd/100 ml whole blood is a tentative no-effect level for long-term exposure. These values apply to adult male workers, and the thresholds may be inappropriate for other groups, such as older persons. (15 Refs)

300. OPTIMAL MANAGEMENT OF ASYMPTOMATIC WORKERS AT HIGH RISK OF BLADDER CANCER

Schulte PA, Ringen K, Hemstreet GP
National Institute for Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, OH 45226.
J Occup Med; 28(1):13-7 1986

Many cohorts of industrial workers at increased risk of occupationally induced bladder cancer are still in the preclinical disease stage. A large proportion of workers in these populations have been exposed to aromatic amines, but have not yet experienced the average latent period for bladder cancer. A need exists for definition of what constitutes optimal management for asymptomatic workers in these cohorts. Promising advances in the epidemiology, pathology, detection, and treatment of bladder cancer pressure for a reassessment of current practices and the application of the most current scientific knowledge. Some of these apparent advances, however, have not yet been rigorously evaluated. The time has come to evaluate these advances so that their application can occur while high risk cohorts are still amenable to and likely to benefit from intervention. This commentary calls for such a n evaluation leading to a comprehensive approach to managing cohorts at high risk of bladder cancer.

301. ADVANCES IN GENETICS AND IMMUNOLOGY: THE IMPORTANCE OF BASIC RESEARCH TO PREVENTION OF OCCUPATIONAL DISEASES (56 Refs)

Omenn GS
Arch Environ Health; 39(3):173-82 1984

Keywords (MeSH): Acetyltransferases/metabolism; Alpha 1-Antitrypsin/deficiency; Aryl Hydrocarbon Hydroxylases/biosynthesis; Bladder Neoplasms/chemically induced; Carboxylic Ester Hydrolases/metabolism; Drugs/metabolism; DNA Repair; Glucosephosphate Dehydrogenase Deficiency/familial and genetic; Human; HLA Antigens/analysis; Liver/enzymology; Male; Mutagens; Occupational Diseases/*familial and genetic/immunology; Oncogenes; Review; Sickle Cell Trait/complications.

302. PREVENTIVE ONCOLOGY IN BLADDER CANCER: DETECTION OF CARCINOGENS IN THE URINE

Harzmann R, Gericke D, Bichler KH
Urologische Abteilung, Universitatsklinik, Calwerstrasse 7, D-7400 Tubingen, W. Germany
Helv Chir Acta; 49(3/4):409-414 1982

Possible mutagenic effects of carcinogens in the urine were tested in experimental and clinical studies. Carcinogenicity was measured in vitro by counting revertant mutations of histidine-dependent Salmonella typhimurium back to the wild-type histidine-independent form in vitro. Twenty dogs and 20 rats were treated with the nitrofurantoin-derivative N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT). Urine was obtained from these animals, as well as from 28 patients with bladder cancer, 16 phenacetin abusers, and 31 chain smokers. Colonies of S typhimurium strains TA 98, 100, 1535, and 1537 were exposed to urine samples. Untreated cultures and cultures treated with standard mutagens served as controls. Colonies treated with urine from the experimental animals showed a significant increase in the frequency of revertant mutations when compared with untreated controls. Strain TA 100 was the most sensitive to mutation. No significant differences were found between cultures with and without S9 microsomal activation. Urine from bladder cancer patients did not increase the frequency of mutation; individual findings varied, however. Urine from chain smokers raised the mutation frequency; the increase was greater with S9 microsomes, but the difference was not significantly different

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from cultures without S9. Urine from phenacetin abusers showed the greatest increase in mutation frequency; addition of S9 produced a great increase over cultures without S9. The mutagenic action is therefore probably due primarily to metabolites of phenacetin, rather than phenacetin itself. The S typhimurium model is evidently a sensitive method for detecting carcinogens in urine. (7 Refs)

303. NEW DIRECTIONS IN CANCER CONTROL

Greenwald P
NCI, DRCCA, Building 31, Room 4A32, Bethesda, MD, 20205
Johns Hopkins Med J; 151(5):209-213 1982

Cancer control is the reduction of cancer incidence, morbidity, or mortality through an orderly sequ ence from research on interventions to systematic application of the results to populations. To help ensure this progression, a system of classifying cancer control research into phases has been developed. The phases are hypothesis development, studies of methods, case-control studies, defined population studies, and demonstration-implementation. Studies of the potential impact of cancer control measures in defined populations are particularly needed. New research support should therefore be provided to research units focusing on this area of cancer control. A new community clinical oncology program will link community physicians with cancer center and university scientists in a cooperative cancer control effort. Another new cancer control program is called chemoprevention research, that is, clinical trials aimed at determining whether selected micronutrients or synthetic compounds can reduce the incidence of cancer. (Author abstract) (17 Refs)

304. GROUPING OCCUPATIONS ACCORDING TO CARCINOGENIC POTENTIAL: OCCUPATION CLUSTERS FROM AN EXPOSURE LINKAGE SYSTEM

Hoeb CC, Walker AM, Hoar SK
Department of Epidemiology, Harvard School of Public Health, Boston, MA
Am J Epidemiol; 117(5):575-89 1983

An occupational clustering scheme has been developed from an occupation and exposure linkage system. In this scheme, occupational titles are grouped together hierarchically according to the numbers and degrees of their shared exposures. The use of the clusters obtained from this hierarchy is demonstrated in the analysis of the data from a case-control study of bladder cancer.

305. PROGNOSIS OF PRIMARY TUMORS OF THE BLADDER (202 Refs)

Bittard M
J Urol (Paris); 91(6):320-400 1985

Keywords (MeSH): Aged; Alkylating Agents/toxicity; Amines/adverse effects/metabolism/toxicity; Animal; Antineoplastic Agents/therapeutic use; *Bladder Neoplasms/chemically induced/etiology/immunology/occurrence/pathology/prevention and control/therapy; Carcinoma, Transitional Cell; Clofibrate/toxicity; Epithelium/pathology; Female; France; Human; Hyperplasia; Male; Middle Age; Nitrosamines/toxicity; Occupational Diseases/chemically induced/economics/prevention and control; Occupational Medicine/standards; Prognosis; Retinoids/therapeutic use; Review; Saccharin/toxicity; Schistosomiasis Haematobia; Tryptophan/toxicity; Workmen's Compensation/legislation and jurisprudence.

306. EFFECTS ON THE LIVER OF CHEMICALS ENCOUNTERED IN THE WORKPLACE

Pond SM
Northern California Occupational Health Center, Building 30, 5th Floor, San Francisco General Hosp. Medical Center, 1001 Portrero Ave., San Francisco, CA, 94110
West J Med; 137(6):506-514 1982

Effects on human livers of three chemicals (carbon tetrachloride, vinyl chloride, and polychlorinated biphenyls) that can be regarded as prototypes of a number of other compounds and illustrate many o f the concepts fundamental to understanding the effects of chemicals on the liver, are reviewed. Many compounds fall into this category and hepatotoxicity may be only one facet of their effect; 2-naphthylamine produces hepatocellular carcinoma in mice but bladder carcinomas in humans. (53 Refs)

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SUBJECT INDEX

This index is constucted from the National Library of Medicine's Medical Subject Headings (MeSH) which are associated with each abstract included in this publication. These MeSH terms can be used to retrieve similar information from the National Cancer Institute's online database CANCERLINE. The asterisk indicates that the concept indexed is a major point of the article. Bold-faced numbers refer to abstracts which are not indexed with a more specific related term and which may represent articles which are rather more general than the rest. For example: "Carcinogens....2, 17, **39**"; where abstracts numbers 2 and 17 would be indexed to a more specific concept under "Carcinogens", such as "Benzo(a)pyrene", but abstract 39 would be indexed only to the level of detail of "Carcinogens".

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